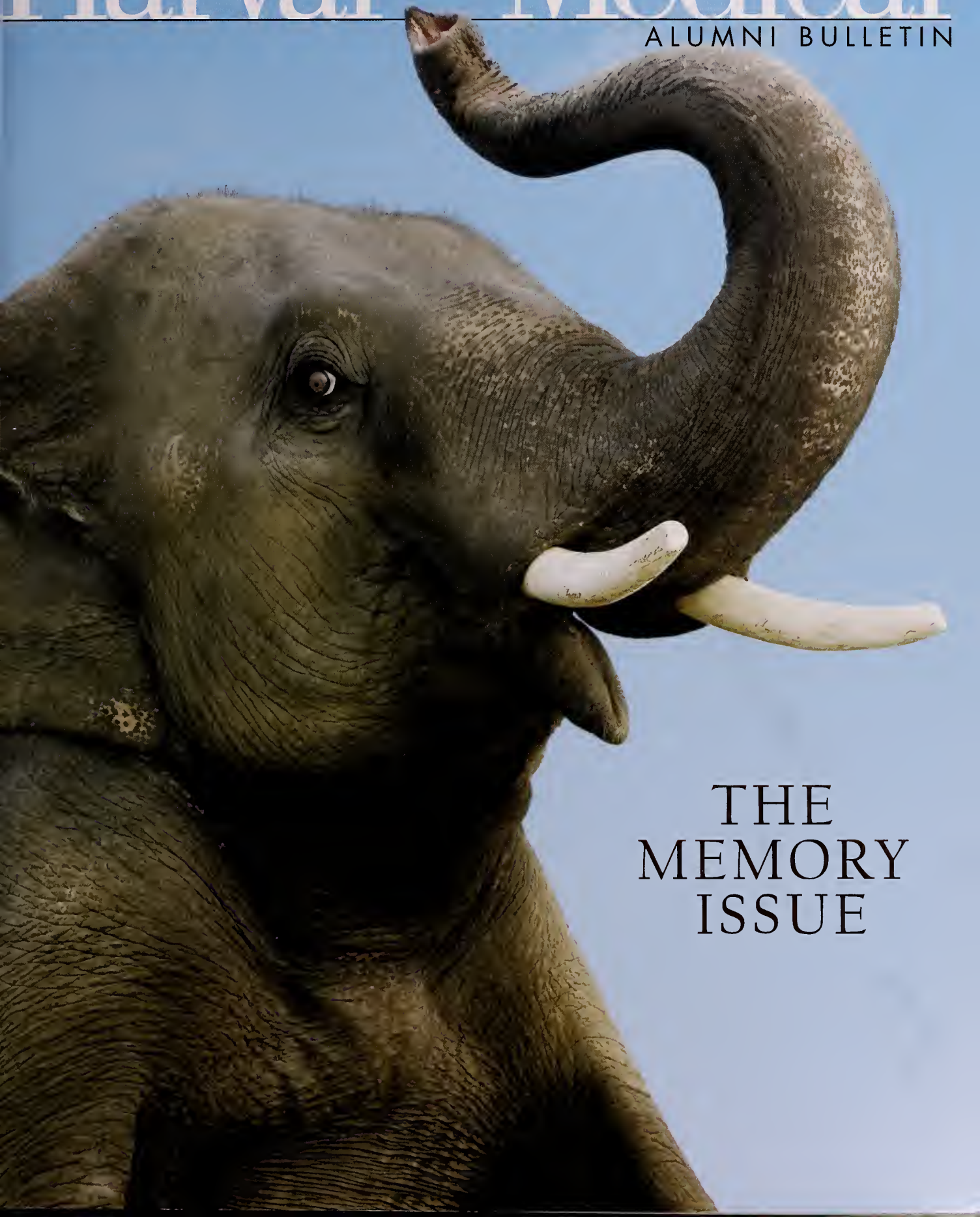
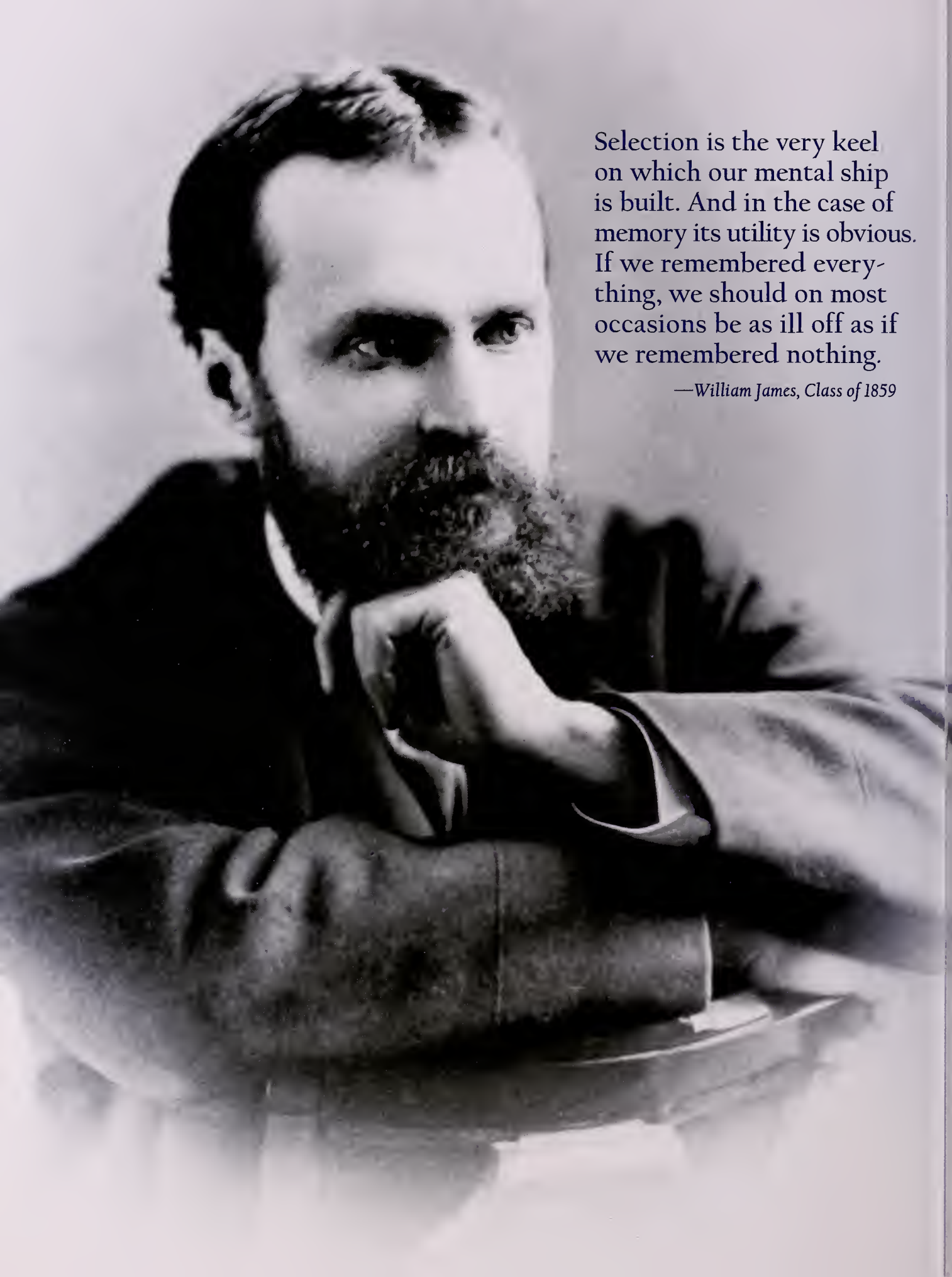
AUTUMN 2008

Harvard Medical

ALUMNI BULLETIN



THE MEMORY ISSUE



Selection is the very keel on which our mental ship is built. And in the case of memory its utility is obvious. If we remembered everything, we should on most occasions be as ill off as if we remembered nothing.

—William James, Class of 1859

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In This Issue

SOON AFTER DR. WATSON AND SHERLOCK HOLMES BECAME ROOMMATES, THE physician had occasion to mention to the detective that the earth revolves around the sun. This information was unwelcome to the latter, who promptly said, "Now that I do know it I shall do my best to forget it." Holmes then elaborated: "I consider that a man's brain originally is like a little empty attic, and you have to stock it with such furniture as you choose. A fool takes in all the lumber of every sort that he comes across, so that the knowledge which might be useful to him gets crowded out . . . [and] he has difficulty in laying his hands upon it."

I read *A Study in Scarlet* well over 50 years ago and remember only this passage, a bit of lumber that thumped to the floor of my brain at the time and has never been swept away, whereas all the rest—the story itself—has been vacuumed off. Why this snippet persisted in memory I don't know. I was in school, and perhaps some small part of my amygdala was aroused by the horrifying thought that my efforts to conjugate Latin verbs, sort out the faults of Franklin Pierce from those of James Buchanan, or come to terms with pi bonds were a fool's errand. In any event, I have come to realize that I am not the custodian of my own attic.

Holmes had it partly right, although the attic may be a great deal bigger than he surmised and its conscious management more difficult. There are people, very few of them, who live with a vivid, day-by-day mental chronicle of their lives and can say in a moment what they were wearing on September 14, 1982, or, reversing the task, tell you on what date Princess Grace died. This ability does, however, seem to drain off some of the brain's reserves. None of the known people with this hyperthymestic syndrome has led a life of otherwise remarkable accomplishment.

Perhaps it is forgetting, not remembering, then, that we should cultivate, and having good filters is what we should aspire to. As George Eliot wrote, "If we had a keen vision and feeling of all ordinary human life, it would be like hearing the grass grow and the squirrel's heart beat, and we should die of that roar which lies on the other side of silence. As it is, the quickest of us walk about well wadded with stupidity."

William Ira Bennett

Gator Aid

We write to supplement the mention of Deborah German '76 in Ann Marie Menting's "The Dean Counter" in the Autumn 2007 issue. We strongly identify with Dr. German's characterization of the physicians she intends to educate and mentor in her role as dean of the new College of Medicine at the University of Central Florida. We are especially delighted because Nemours Children's Hospital, a new pediatric specialty facility, will be located near the medical school. We hope that as the hospital becomes part of Central Florida's expanding health services resources, we will be able to make a solid contribution to the "good doctors" that Dr. German will help nurture. We wish her the best and applaud her for being more fearful of not pursuing this important goal than she is of failure.

DAVID J. BAILEY, MD, MBA,
THE NEMOURS FOUNDATION
JOHN NOSEWORTHY '70, FACS, FAAP,
THE NEMOURS PARTNERSHIP FOR
CHILDREN'S HEALTH
JACKSONVILLE, FLORIDA

Spreading the Health

In response to "The Dean Counter," I'm proud to share the story of one of your alumni. In 1978, Rodolfo Herrera Llerandi '42 founded the Universidad Francisco Marroquín Medical School in Guatemala with the same mission as HMS: to seek excellence. By doing this, Dr. Herrera, now emeritus dean, was able to transfer the skills of his hands to the hands of the more than 500 doctors who have since graduated from UFMMS.

Dr. Herrera's leadership has shaped UFMMS into an institution that maintains the high standards required to meet twenty-first century needs—a worthy goal for a "daughter" of HMS. Now 95 years old, Dr. Herrera keeps inspiring us to pursue what doctors are for: to heal and support patients efficiently, respectfully, and with love.

RODRIGO BOY, MD
GUATEMALA CITY, GUATEMALA

BATTEN DOWN THE HATCHES



"What Are Doctors For?" in the Autumn 2007 issue of the *Bulletin* touched close to home. Nearly two years ago I ended my overtaxed primary care practice at Massachusetts General Hospital, where I was one of the two busiest general internists, and started Orchard Health Care, a membership practice that more effectively serves about one-quarter the number of patients I had previously. As part of that transition, I rejoined the Beth Israel Deaconess network, which enthusiastically supports such "boutique" medical practices.

The many patients who continued with me (and the new ones who joined) are pleased with the calmer and more detailed care and advice they receive. My staff is no longer frayed. I am no longer pressed so hard, nor do I have to move so quickly that I fear I will miss important medical data. I have regained my joy in the art and practice of medicine.

I am acutely aware of the socioeconomic issues that membership practices raise, but I am more concerned about the economic starvation diet that a confederation of insurers and government regulators have forced on primary care for the past two decades. Primary care is dying. The shortage of primary care physicians is critical in Massachusetts and elsewhere—and no solution is in sight. Medical students, even those attracted to internal medicine, look to other specialties to receive fair compensation for their skills and to enjoy a reasonable life. For the ten years I precepted in the primary care clerkship at HMS, not one of the talented students I worked with went into primary care.

My patients and I have escaped the shipwreck that primary care has become through the membership model, where patients pay me an annual fee so I can afford to see hundreds rather than thousands of patients. My earnings are now comparable to those of the average dermatologist or orthopedist. This is my micro-solution, but it is not a macro-solution for a core problem in U.S. medicine today: the demise of primary care. Where is our medical school on this issue? Where are the medical societies?

Perhaps we want a care system built on nurse practitioners and "disease management" telephone staff collectively trying to replace the primary care role, an alternative that is inferior across the board on cost, quality, access, and patient satisfaction. The good ship primary care is foundering on economic rocks. Prompt action might save it. But more likely our studied ignorance of the economic forces destroying primary care will continue, and we'll soon be looking around and asking what happened. We'll wonder why there are no primary care physicians, and why medical care has become more expensive, more disjointed, and less effective.

HMS is a world leader in medical research and policy. It should take a dramatically more active role in spotlighting the disintegration of primary care and in promoting changes in the regulatory and economic policies that are destroying the keystone of our medical care system.

STEVEN R. KANNER '69
WALTHAM, MASSACHUSETTS

The Envelope, Please

ON THE 56TH ANNUAL MATCH DAY IN March, the 168 members of the HMS Class of 2008 gathered to receive their much-anticipated white envelopes—the contents of which revealed where the fourth-years would be spending the first year of their residencies. Nearly half the graduates have remained in Massachusetts for at least part of their residencies, while 23 percent have headed to California and 7 percent have gone to New York. Internal medicine remained the most popular specialty, with 27 percent of the class matching in this field. Pediatrics was the second most chosen specialty area.



PHOTOS: STEVE GILBERT

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CONNECT THE DOCS

Harvard Launches the Catalyst Website

Harvard Catalyst, a University-wide initiative aimed at improving human health, was rolled out this year. The enterprise seeks to engage faculty and students at Harvard's ten schools and eighteen academic health care centers. To assist that effort, Harvard Catalyst recently unveiled its new website. The site allows investigators to form cross-institutional teams, gain access to tools and technologies, and obtain seed funding for projects. Harvard Catalyst is funded by a five-year, $117.5-million Clinical and Translational Science Award from the National Institutes of Health and an additional $75 million from HMS, other Harvard schools, and affiliated hospitals. To learn more, visit http://catalyst.harvard.edu. ■



Life After Harvard

SINCE LEAVING BOSTON FOUR YEARS AGO TO TAKE MY current position in Philadelphia, I am often asked what life is like after Harvard. In fact, I feel like I haven't really left, in part because I maintain a faculty appointment at HMS and often return to teach medical students and residents, and in part because I'm serving as president of the Harvard Medical Alumni Association.

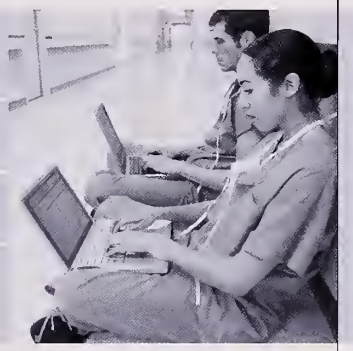
At our Alumni Council meetings, we hear about all aspects of the School—from broad strategic priorities down to the details of curricular reform and student debt. At the same time, we discuss how the Council can best work with the School for the benefit of all relevant parties—alumni, students, and the School itself. So I've only partially severed my ties, and I treasure the ones that remain intact.

Still, I don't think anyone who has gone through the extraordinary experience of education at HMS ever completely loses the connection. Whatever career path we ultimately choose, we recognize how strongly our professional lives have been shaped by our education, our experiences, the contacts we made during our time as students, and any additional training or relationships we have maintained with the School. During our 35th HMS reunion in June, my classmates and I reinforced the bonds we had forged decades ago, bonds that hadn't really broken despite many years and many miles of separation.

Throughout the past year, William Chin '72 (my predecessor as president of the Alumni Association), JudyAnn Bigby '78 (my successor), and I have discussed ways in which the Council could help strengthen the links among alumni, between alumni and current students, and between alumni and the School. As we know from social networking sites such as Facebook, electronic communication through the Web provides us with an unprecedented opportunity to establish a virtual HMS community that extends far beyond campus. Bill, JudyAnn, and I have joined other Council members in recognizing that developing the platform and the infrastructure for such a community—and then encouraging alumni and students to become active participants—is more than a one-year project. We believe, however, that it's an important priority.

What is our vision for this virtual community? Ultimately, it will allow alumni to connect with each other and with students around areas of common interest, ranging from clinical and research interests to volunteer opportunities. Students will be able to link with alumni who have specific interests or live in particular geographic areas. Students will also have opportunities to seek advice, establish mentoring relationships, and find alumni willing to provide housing during travel for residency interviews. Ideally, the community would also provide a portal for alumni to experience some of the current curriculum, perhaps through access to digitized lectures or other educational resources. We are in the early stages of exploring the potential applications of such a community, and a range of unanticipated applications will undoubtedly emerge as alumni and students recognize the promise and power of this new community.

Ultimately, the virtual community will allow alumni to link with each other and with students around areas of common interest, ranging from clinical and research interests to volunteer opportunities.

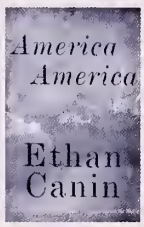


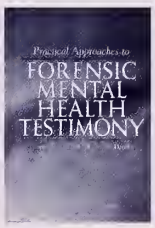
Our priorities now are to develop the infrastructure for the virtual community and to establish a robust database of all alumni. We will work with the School to determine how such a resource is best developed, housed, and financed within the complex organizational structure of Harvard. I have discussed this priority with Dean Jeffrey Flier, and he shares our interest and excitement.

So, in returning to the question of whether there is life after Harvard, my hope is that the question will become moot as we use the power of the Internet to help all alumni feel connected to the HMS community for life. ■

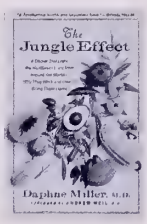
Steven E. Weinberger '73 is senior vice president for medical education at the American College of Physicians in Philadelphia. He can be reached at sweinberger@acponline.org.



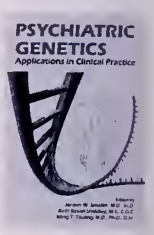












The Spirit of the Place

by Stephen Bergman '73 (as Samuel Shem) *(Kent State University Press, 2008)*

This novel from the author of *The House of God* follows an expatriate doctor who returns to his small hometown after his mother's death. While there, he reunites with family, comes to terms with old rivals, and reconnects with the town doctor who once mentored him. Bergman's tale underscores the link between the health of individuals and their communities and reveals what it means to be a healer—and to be healed.

America America

by Ethan Canin '92 *(Random House, 2008)*

Set in a small town during the Nixon era and today, Canin's sixth novel tracks the journey of Corey Sifter from yard boy on the estate of a powerful local family to aide to a presidential candidate. As the candidate's campaign gains momentum, Sifter finds himself caught in a web of events in which loyalty, politics, sex, and gratitude conflict with morality, love, and truth.

Practical Approaches to Forensic Mental Health Testimony

by Thomas G. Gutheil '67 and Frank M. Dattilio *(Lippincott Williams & Wilkins, 2007)*

This practical guide provides concrete approaches to help professionals prepare for court appearances as mental health experts without losing their perspective, integrity, or sense of humor. The book includes excerpts of actual direct and cross-examinations, accompanied by suggestions for improved responses.

The Mercy Rule

by Perri Klass '86 *(Houghton Mifflin, 2008)*

What makes a good parent—and who should judge that? These are questions posed in Klass's novel about Lucy, a foster-care survivor dealing with similar families in her work as a pediatrician. As Lucy tries to balance the struggles of her patients with those of her own family, she must judge herself as a parent, critique other parents, and deal with the echoes of her childhood.

The Jungle Effect

A Doctor Discovers the Healthiest Diets from Around the World—Why They Work and How to Bring Them Home, by Daphne Miller '93 *(HarperCollins, 2008)*

Miller discusses various "cold spots" around the world in which certain chronic diseases are uncommon—rates of depression are lower in Iceland, for example—and she explains how following indigenous diets can help readers regain health and wellness. The book includes inspirational stories from Miller's patients, interviews with world-renowned food experts, and indigenous recipes. Andrew Weil '68 provides the foreword.

Effective Management of Health and Safety Programs

A Practical Guide, by Royce Moser, Jr. '61 *(Third Edition, OEM Press, 2008)*

Moser's guide stresses how to design, implement, evaluate, and obtain support for health and safety programs by examining practical management techniques and applications. The updated text contains five new chapters on subjects such as productivity enhancement, entrepreneurship, and planning health care responses to mass casualty situations. The author also includes examples of lessons learned the hard way to help readers avoid similar mistakes.

Psychiatric Genetics

Applications in Clinical Practice, edited by Jordan W. Smoller '91, Beth Rosen Sheidley, and Min T. Tsuang *(American Psychiatric Publishing, 2008)*

Written explicitly for practitioners, this book is the first to focus on the clinical applications of genetics in psychiatry. The editors explore issues involved in genetic counseling, the interpretation of familial and genetic information for clinical use, information about the risks associated with specific psychiatric disorders, the uses of genetics testing, and the risks and benefits of medication use during pregnancy. The editors also cover ethical, legal, and social implications to help illustrate the dilemmas that arise with advances in genetics research.

Spiritual Evolution

A Scientific Defense of Faith, by George Vaillant '59
(Broadway Books, 2008)

RECENTLY, A 44-YEAR-OLD SOMALIAN REFUGEE WAS brought to the clinic by his group home staff, led through the door by the hand. His psychosis had begun in the camps, where he would wander away from the safe zones. Years have passed, his country has changed, and he is wandering still, away from group homes, from hospitals, and from his small family. He repeats words if they are gently said to him, but otherwise speaks only to himself. What he saw in Somalia has caused him to lose his mind.

He was in my mind when I read George Vaillant's most recent book, *Spiritual Evolution: A Scientific Defense of Faith.* Every psychiatric resident—and any humanist—should know about Vaillant '59, who has led Harvard's Study of Adult Development for the past three decades. Based on longitudinal data of the lives of more than 700 men, Vaillant has given us the concept of higher coping defenses and proof that early tragedy need not conscript the future. He is a great and optimistic thinker.



Perhaps because he is aging like the rest of us, Vaillant's more recent preoccupations have grown wings. He remains optimistic, but now he is thinking less about men and more about mankind. In *Spiritual Evolution,* he wants to convince the reader that "positive emotions are not just nice to have, they are essential to the survival of *Homo sapiens* as a species." He doesn't expect us to take his word. He presents two hundred pages of proof from genetic, anthropological, and developmental sciences. From every angle, he makes a case for the "strong causal association between positive emotions and post-crisis resilience." But again I thought, with some doubts, of my patient.

The essential positive emotions Vaillant writes about—neither the American Psychiatric Association nor Freud ever showed much interest in them—are faith, love, hope, joy, forgiveness, compassion, gratitude, and awe. They derive neuroanatomically from deep limbic and more superficial frontal systems, which have become linked in man through evolution. Unselfish love, for instance, is a limbic product; it evolved in the brain over millennia "to facilitate...attachment, social cohesion and spiritual community." Hope, on the other hand, is frontal, and a bit more cerebral—it requires a comprehension of time, past and future.

The positive emotions are parasympathetic; vessels dilate, heart rate calms, oxytocin flows. We feel empathic, relaxed, and communal-minded. In contrast, negative emotions such as fear and anger—which some might argue also are essential—cause us to feel cramped and self-serving. They are physiologically catabolic. The woeful restating here is mine—Vaillant uses much greater sophistication and intelligence to lay out the details. Still, we all get the point, and, given a choice, know which feelings we would put our money on.

Each emotion receives a chapter, explaining its many healthful, fruitful facets. It is as if the author is rotating cut diamonds to view them from all angles. This results in some excellent cocktail party facts—for instance, "two tablespoons of gray matter were added [to primate brains] every 100,000 years"—and some lovely poetic notions: "compassion is the desire to separate someone, even if unappealing, from his suffering"; "forgiveness increases steadily from age 3 to age 90."

But being human, Vaillant writes, we also struggle against ourselves. With the development of language, we gained poetry and logic, science and measurement, at the expense of spirituality or proper regard for these essential feelings. Science itself has had little interest in studying them. And traditional fundamentalist religions have excluded "the amalgam of positive emotions that bind us to other human beings." Instead, these religions are mostly "dry cognitive questions about patriarchal gods and 'me,'" not the inclusive social communities that will save us.

Any encompassing theory of humanity has to make room for evil. In his book, Vaillant addresses it with brevity, as a force whose time has more or less come and gone. He points out that the Nazis "lasted barely a decade, but after 1,500 years the Benedictine Order is still alive and well." This may be true, but it made no difference to the victims, or to my own devastated and wandering patient. Natural selection, cultural anthropology, and moral development did nothing for them. That is the sadness of theories. They cannot fit us all.

Vaillant writes with such charisma and personal passion, such optimism after so many decades in the people business, that sometimes *Spiritual Evolution* teeters on the precipice of self-help. But then he catches himself. "As soon as my writing becomes proscriptive," he admits, "as soon as I suggest that I *know* how or why spiritual enlightenment and mystical experiences develop, I have lost my way."

Ah, I thought with relief, that is the conclusion of a wise man. ■

Elissa Ely '88 is a psychiatrist at the Massachusetts Mental Health Center.

Double Trouble

Although much has been learned since Alois Alzheimer first identified abnormal plaques and tangles in the brain of a woman with dementia, treatments for Alzheimer's disease remain largely ineffective and diagnostics inadequate. New research from a collaboration led by an HMS professor may help address these shortcomings.

Using extracts from human brain tissue, Dennis Selkoe, the Vincent and Stella Coates Professor of Neurologic Diseases in the Department of Neurology at Brigham and Women's Hospital, and colleagues showed that a two-unit peptide of human amyloid-beta protein (Aβ) can induce the synapse dysfunction and loss that are hallmarks of early-stage Alzheimer's. This dimer is the smallest configuration possible for the protein. The study, published in the August issue of *Nature Medicine*, provides insight into how the disease begins in the human brain and how it might be treated.

"All forms of Aβ are bad news," says Selkoe. "You don't want it to build up. But smaller assemblies are worse." Such assemblies are the first ones to form when the body produces excess Aβ.

The results are compelling; until now, evidence of the protein's involvement in Alzheimer's came only from model experimental systems in which synthesized forms of Aβ or Aβ produced from cell cultures were used. "That's fine," says Selkoe. "But why don't we go right to the source?"

Source Material

Selkoe and coauthor Ganesh Shankar '10 did just that by starting with donated brain specimens from deceased patients who had some form of dementia. Shankar extracted material from these brains and found substantial amounts of soluble Aβ in the Alzheimer's brains, but little in the others.

Soluble Aβ oligomers may float freely inside the brain's fluid-filled extracellular spaces. Over time, these soluble complexes form insoluble fibrils that are deposited as amyloid plaques. The research team elected to focus on the levels of soluble Aβ. Previous research had shown these levels correlate most strongly with cognitive symptoms in Alzheimer's disease.

The scientists found that soluble Aβ that was extracted directly from the human cortex was a potent inhibitor of long-term potentiation, a neural mechanism important to the formation of new memories, in the hippocampus of normal mice. Soluble Aβ also facilitated long-term synaptic depression, essentially priming hippocampal neurons to tune some signals out.

Unkind Cuts

To test the effects of soluble human Aβ on the synapse, Shankar and Selkoe connected with Bernardo Sabatini '95, an HMS associate professor of neurobiology. In 2007, Sabatini and Shankar showed that soluble Aβ from cultured cells disrupted synaptic spines. In this new work, Shankar and Sabatini repeated those experiments using soluble Aβ oligomers from Alzheimer's brains. Again, they observed synapse loss. According to Sabatini, the human Aβ oligomers appear to be activating a normal pathway and biasing it toward synapse loss.

The team then collaborated with researchers at the University College Dublin to test the human peptide's effect on behavior. The scientists injected the brains of rats with either a sample of soluble human Aβ or a sample from which the Aβ had been removed. Although the rats in the experiment had previously



been trained to avoid a dark chamber, exposure to the soluble form caused the rats to go back into the dark chamber as if they had never been trained.

The group then turned from free-floating Aβ assemblies to the largely insoluble amyloid plaques, also extracted from the brains of humans with Alzheimer's disease. The researchers found some good news: Isolated plaques generally did not exhibit biological activity on synapses. Instead, they seemed to act as reservoirs that collect and sequester smaller amyloid assemblies, thereby keeping toxic Aβ oligomers out of circulation. This suggests that plaques, though they may have some pathologic effects, are not principally involved in initiating early synaptic impairments in Alzheimer's disease.

Selkoe believes, however, that plaques have a maximum capacity. Once that capacity is reached, he says, excess free-floating assemblies, including toxic soluble dimers, have nowhere to go and so are free to diffuse into synaptic clefts and cause injury.

Shankar and Selkoe also undertook experiments to chemically isolate Aβ isoforms from the human brains used in the study. They found Aβ exists in many different-sized forms. In addition, they found the soluble human Aβ dimer inhibited long-term potentiation while monomers and other higher-order assemblies did not affect this form of synaptic plasticity.

Shankar has tested several potentially therapeutic Aβ antibodies and found that targeting dimers may be effective, with those directed to the peptide's N-terminus most effective at neutralizing the dimers' adverse effects. Unpublished results of a trial of a humanized version of the same antibody reported by other researchers also showed positive clinical benefits in certain Alzheimer's patients in the mild to moderate stages of disease. ■

Elizabeth Dougherty is a science writer for Focus.

Regulatory Concerns

THE THYROID GLAND CAN BE a capricious organ, spilling out too much or too little of its vital hormones. An excess or lack can lead to a panoply of debilitating mental conditions. Indeed, physicians will typically check thyroid hormone levels in patients complaining of memory loss or depression. It now appears they may have another reason to check thyroid function in their female patients. A new study suggests that women with low or high levels of thyroid-stimulating hormone (TSH) are more likely to develop Alzheimer's disease than those with normal levels.



A team of researchers followed 1,864 participants in the Framingham Heart Study whose thyroid function—and TSH levels—had been measured between 1977 and 1979. Zaldy Tan, an HMS assistant professor of medicine at Beth Israel Deaconess Medical Center, together with colleagues at HMS and Boston University, monitored the participants for an average of 12.7 years and found that women with TSH values in the lowest and highest third—less than 1 milli-international unit per liter or more than 2.1 milli-international units per liter—were twice as likely to develop Alzheimer's disease as those with values in the middle third. Men were not at similar risk.

The researchers, who published their findings in the July 28 issue of *Archives of Internal Medicine*, found an elevated risk even in women who, at some point, had undergone hormone supplementation or suppression therapy, suggesting the effects of low and high TSH levels may be irreversible.

The finding that puzzles the researchers is that only women were vulnerable to the effects of aberrant hormone production. In fact, women appear to be more vulnerable to other thyroid-associated conditions, such as Graves' disease.

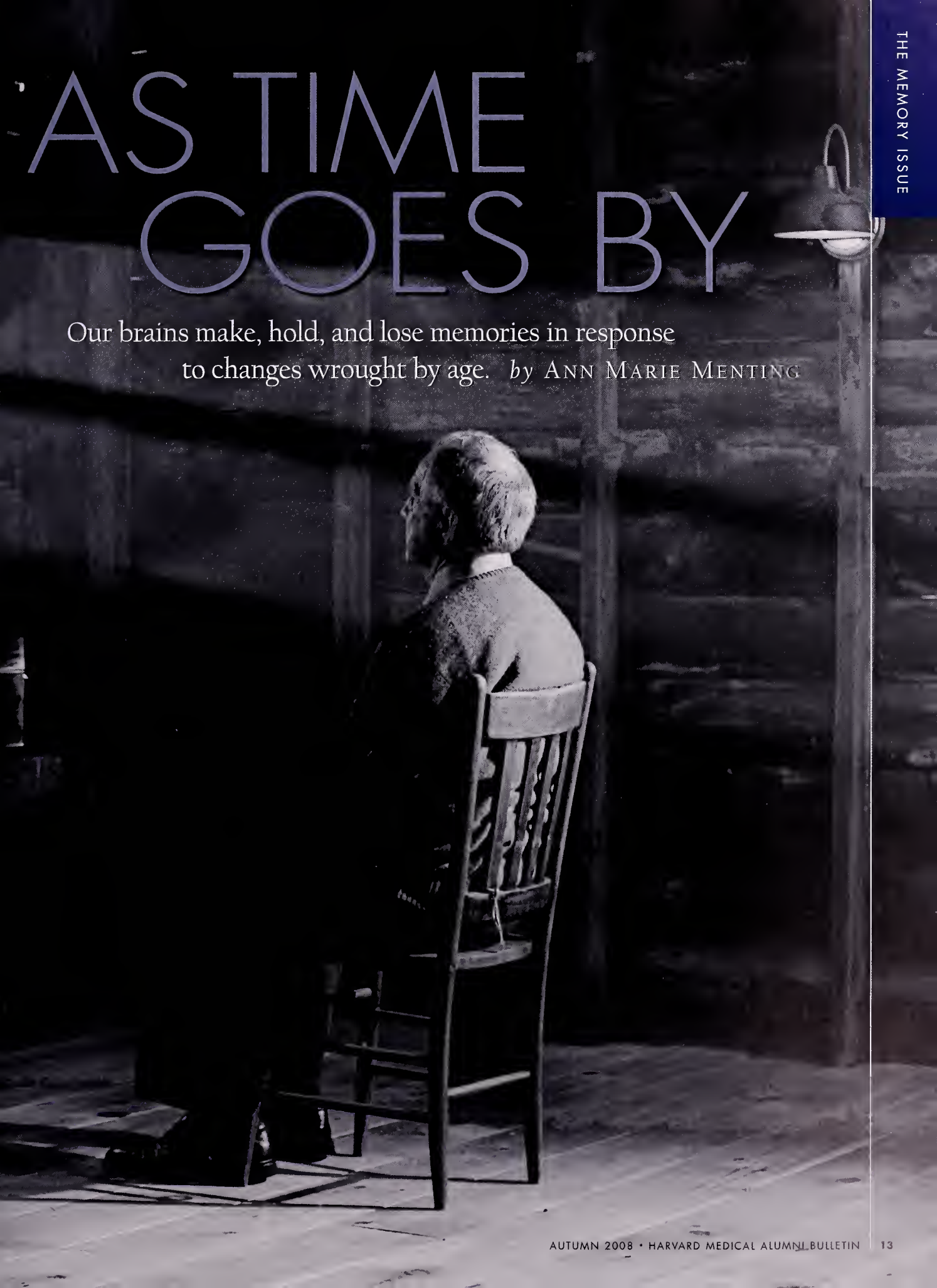
As to how this dysregulation links to Alzheimer's disease, the investigators pose an intriguing hypothesis. According to Tan, too little or too much thyroid hormone could lead to irregularities in the regulation of the amyloid precursor protein gene, which is controlled by TSH and known to play a role in Alzheimer's. Abnormal levels may cause aberrant production of plaque-causing amyloid proteins. ■

Misia Landau is the senior science writer for Focus.



AS TIME GOES BY

Our brains make, hold, and lose memories in response to changes wrought by age. *by* Ann Marie Menting



ALL WE DO IS IS BASED ON A MEMORY. EACH thought, each movement, each conversation draws upon the library of life that is nestled within our brains. From the moment of our birth until the moment we die, our brains, with their billions of neurons and trillions of neuronal connections, gather, package, and store the sensory information transmitted by our eyes, ears, nose, and skin so that we may access and apply it to the physical, intellectual, and social demands of the world we inhabit.

Yet, just as our muscles change with age, so, too, do our brains. Small wonder, then, that explorations into how age-related changes affect our brains—and, by extension, the ways we engage with our world—have so captivated researchers, observers, and those who simply hope to keep the old bean keen.

Down Memory Lane

In 1906, the Spanish anatomist Santiago Ramón y Cajal received a Nobel prize for his "neuron doctrine." Neurons, he said, function as discrete units. Each cell body receives signals from a rootlike array of dendrites and transmits those signals along an axon to the waiting dendrites of other neurons. Researchers later showed that transmissions from axon to dendrites occur across synapses and that neurotransmitters—substances such as dopamine, acetylcholine, and serotonin—help signals jump these clefts.

The idea that neurons form networks that orchestrate our ability to build memories was posited in 1949 by Canadian psychologist Donald Hebb. From his studies of how the brain commanded behavior, Hebb postulated that when one neuron repeatedly caused another neuron to fire, a type of metabolic bonding occurred. His idea spawned a slogan: Neurons that fire together wire together. This fire–wire partnership, researchers later discovered, results in networks of connected neurons, each a memory trace of a learned experience that expands or modifies other traces.

When functioning efficiently, the more than 100 billion neurons in the adult brain provide access to a phenomenal cache of information. Researchers have found that it is the degree to which our aging, changing brains construct new connections between these neurons—and avoid or minimize the destruction of existing ones—that determines the scope and vitality of these networks.

"The aging process does not appear to be a passive one," says Bruce Yankner, a professor of pathology and neurology at the Paul F. Glenn Laboratories for the Molecular Biology of Aging at HMS. "It instead appears to be a balance between stress and compensation."

One of the leading theories for how the brain confronts age-related changes is the concept of synaptic plasticity. This theory holds that our brains continually remodel themselves, tweaking the number of connections to other neurons so as to embrace new information, eliminate links to unused networks, and reflect new complexities associated with information in other traces.

"Synaptic plasticity truly is an exciting concept because it says the brain is not a fixed structure," says Majid Fotuhi '97, an assistant professor of neurology at the Johns Hopkins University School of Medicine and director of the Center for

Memory and Brain Health at Sinai Hospital's LifeBridge Health Brain & Spine Institute. "One cell may have a thousand synapses on it but then something happens—you learn something new—and you might then have a thousand and twenty synapses."

Situations that trigger these types of changes occur constantly. Negotiating a reduction of global carbon dioxide emissions, for example, could trigger synaptic growth. So could preparing dinner.

Let's say you use a particular pot regularly. You know it has a small break in the handle, but it's usable, so you pull it out, fill it with soup, and place it on the stove. After the soup heats, you reach over to pull the pot off the burner. You get burned. A strong signal associated with the pain speeds to your brain, as does the realization that you have touched exposed metal in the handle. Your brain uses this information to establish new connections; you learn to avoid using that pot or to use a potholder when handling it. You have established a memory that, like most memories, helps you function better in your world.

Form and Function

Viewed without its protective bony outer structure or the rugged inner membrane that wraps its mass of cells, the brain's cortex bears an uncanny resemblance to a shelled walnut. This wrinkled, bisected structure is arguably the most sophisticated area of the brain.

Within each cortical hemisphere is tucked a small structure quite active in memory making: the hippocampus. Shaped like a banana, the hippocampus serves as an active way station for information, holding new material that is needed immediately, sending to storage that which will be held for days or decades, and assisting in the recall of data housed in other cortical areas.

The cortex is involved primarily in declarative memory, which captures the facts and events of our lives and allows for their recall in some tangible manner: the spoken word, a visual representation, a gesture. Declarative memory can be held for a short time, as for a one-time use of a telephone number, or it can be held up to a lifetime. And although synaptic plasticity can help keep it robust, biology and environment do conspire to whittle away at it over time.

A second form of memory, procedural memory, primarily engages noncortical areas of the brain, most notably the cerebellum. Procedural memory involves sequential, coordinated movements, such as those associated with riding a bicycle. Unlike declarative memory, procedural memory is rugged and not easily lost to the passage of time. This form of memory is a product of action, an imprint of repetitive, serial movements that can be acquired only through physical participation.

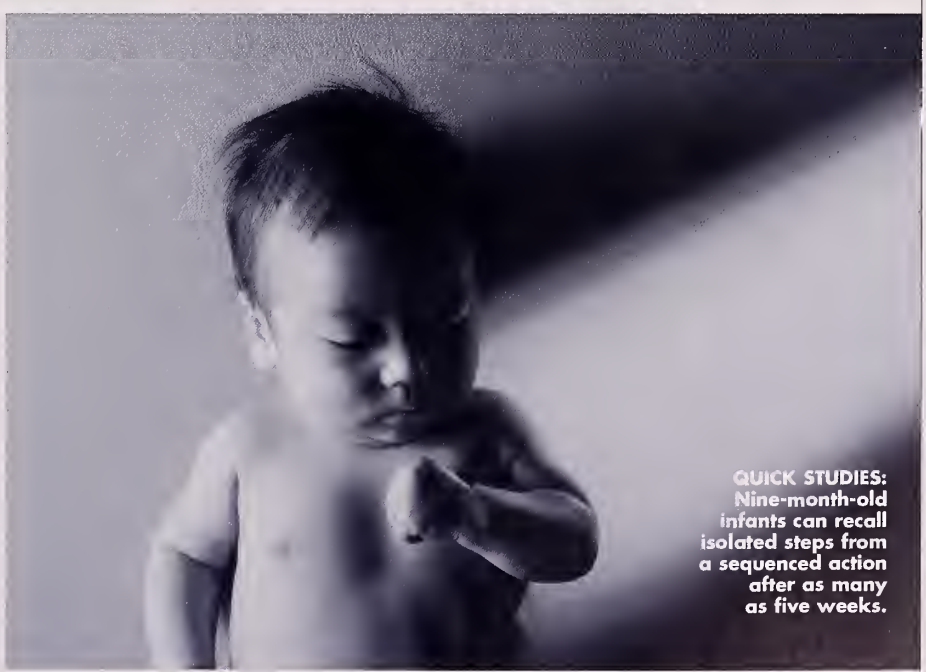
Adjusting the Volume

Age-related changes to our brains influence the speed with which we can access stored information, the complexity of the neural networks that contribute to those memories, and the level of function of certain cortical areas.

The fetal brain produces cells and connections in quantities that far exceed the numbers that will populate the adult brain. As newborns soak up information critical to functioning within their environment, competitive elimination starts to prune away unused or underused cells. Initially, the neurons and synaptic connections, known collectively as gray matter, are focused on taking in information and learning. By six months, however, researchers have found evidence of declarative memory as infants are able to recall one or more steps in a simple sequence of events within 24 hours of having learned them.

In another three months, infants can recall isolated steps from a sequenced action after as many as five weeks. By 14 months, babies can recall several steps of a multi-step action for as long as four months while 20-month-olds can recall all the steps—and their proper order—after six months.

The robust nature of this progression in behavior mirrors a flurry of develop-



QUICK STUDIES: Nine-month-old infants can recall isolated steps from a sequenced action after as many as five weeks.



The brain's cortex bears an uncanny resemblance to a shelled walnut. This wrinkled, bisected structure is arguably the most sophisticated area of the brain.

ment within the structures of the fetal and infant brain. The cells that make up much of the hippocampus form in the first 17 weeks of fetal development and have ordered themselves in the locations they will hold in the adult brain well before birth. Hippocampal synapses also develop quickly; they are present in the fetus by 15 weeks, ramp up their numbers after birth, and reach adult levels by approximately six months.

Certain subdivisions of the hippocampus are slower to develop. An area known as the dentate gyrus, important in consolidating new information, has about 70 percent of its adult complement of cells at birth and achieves full adult morphology after 12 months. Synaptic development in this subregion also lags that for the hippocampus: Between 8 and 12 months, the number and density of its synapses spike to a level above that supported during adulthood. By age five, selective pruning has decreased the number of connections to that found in adults.

Development in other association areas of the cortex mirrors that of the dentate gyrus. Cortical definition begins around 28 weeks of gestation, with synaptic densities in areas critical to association and storage peaking in infants by age two. Around the same time, the number of synapses in the prefrontal cortex tops out. In the mature brain, this cortical region provides temporary mental workspace, known as working memory, for processing decisions that involve complex behavior and problem solving.

Overall, the number and density of synapses most capable of plasticity increase throughout childhood. By age four, however, increases of this gray matter are outpaced by growth in the volume of white matter, the mass of networked neurons whose axons are wrapped in insulating myelin. Myelinated axons propel information up to a hundred times more quickly than their gray matter counterparts, allowing for quicker access and recall of information. In the brain, the period during which its various regions are most actively pruning, myelinating, and maturing—a period of neural growing pains, as it were—coincides with another period known for its awkwardness: adolescence.

Gear Up

"The cortex of a young person," says Zaldy Tan, an assistant professor of medicine at HMS and director of the Memory Disorders Clinic at Beth Israel Deaconess Medical Center, "looks like a complicated mass of wrinkled fat tissue, with numerous peaks flanked by valleys. But as the brain ages, its appearance smoothes out; the peaks flatten and the valleys widen." These topographic alterations are the result of changes to the brain's volume and cellular material.

The ratio of gray matter to white matter begins to shift from age four through early adulthood. Although the precise reason for this has not been found, neuroscientists speculate it may be twofold: an increase in mature, myelinated regions plus the pruning of less productive gray matter synapses. Researchers even have movie-like evidence supporting this conjecture. In time-lapse sequences of gray matter-to-white matter changes, researchers found that the cortical regions in adolescents mature in an order that echoes behavioral progression. First the primary sensorimotor areas along the frontal-to-occipital axis myelinate, then back-to-front myelination occurs from the parietal lobes to the frontal lobes.

The prefrontal cortex, that working memory reservoir useful in decision-making, is among the last to mature. Part of that maturation involves an increase in the role of dopamine, a neurotransmitter critical to deciphering environmental cues when choosing between conflicting options. Inputs for this chemical increase significantly during adolescence. Exposure to dopamine is thought to contribute to the development of our ability to use ideas to achieve a goal rather than simply acting instinctively in a given situation. In broad strokes this means an adolescent's reflexes and keenness of sight and hearing are honed well before the young person's ability to process complex information is.

Even synaptic pruning, which begins in earnest in childhood, changes focus during adolescence. Pruning in the early brain targets low-performing excitatory synapses that transmit information neuron to neuron, a reasonable approach considering the efficiency with which children and early adolescents need to learn. But by late adolescence, pruning zeroes in on inhibitory synapses, which control the flow of information between neurons. Thus, the developing brain grows in its ability to control not only the speed by which signals travel but also the efficiency of their routes. The result: actions grow nuanced so as to, in a sense, reflect a synthesis of information leavened by learning and experience.

All this upheaval calms by age 30, when the number of cell-to-cell contacts achieves an adult pattern and the number of neuronal connections reaches a near steady state—except among adults who prod their brains to do more.

New Tricks

Normal aging in the brain can mean little notable behavioral change for an adult untroubled by trauma to the head, disease that affects the brain, or excessive stresses, whether from responsibility, diet, or lifestyle. Physiological changes do occur—synaptic connections lessen, the volume of certain cortical areas diminishes, and the production of neurotransmitters decreases. Yet the adult brain may actually be able to compensate for these alterations: Some research indicates cor-

tical regions team up to accomplish work previously done individually.

Researchers looking at cross-sectional behavioral data for individuals between the ages of 20 and 80 have found little to no evidence for accelerated declines in the latter decades for such capacities as processing speed, working memory, and the encoding of new declarative memories. There is evidence, however, for linear declines in these areas—as well as in spatial ability and reasoning—beginning by age 40 or 50. In one area, speed of processing, several studies have found a 2 percent decline per decade after age 30.

"The decrease in speed of mental processing that is seen with age is not a problem," says Tan. "The brain may become less efficient, but that doesn't mean it also experiences a decrease in absolute memory."

To tease out secrets to healthy brain aging, Tan is mining a 60-year data trove on the health of another organ: the heart.

"Study upon study has shown that physical activity actually decreases one's risk of cognitive decline with age," Tan says. "But what has really struck me from my work with the Framingham Heart Study is that healthy aging seems to mean that what's good for the heart—a healthful diet, exercise, low cholesterol—is good for the brain, too."

The boost that cognitive health can get from good cardiac health can be augmented by good social health, according to Robert Waldinger '78, an HMS associate professor of psychiatry and director of The Study of Adult Development at Brigham and Women's Hospital.

"There is strong evidence that people who are more connected to others, whether through marriage, friendships, children, or grandchildren, do better physically, cognitively, and emotionally," Waldinger says. "Loneliness, in fact, is considered a risk factor for aging poorly."

But with a finely tuned organ such as the brain, little things can mean a lot. Take genes, whose business it is to oversee our molecular world. Several years ago Yankner looked at the genetic signatures of the brains of people whose ages ranged from 26 to 106. He found that certain genes control the formation of new synaptic connections, others respond to age-induced stresses such as the DNA-damaging molecules known as free radicals, and still others are especially vulnerable to DNA damage. An intriguing possibility is that these genetic characteristics may predict the brain's future.

"We found that gene expression was quite similar among young adults under 40 and somewhat similar among adults over 70," Yankner says. "But those between 40 and 70 showed a good deal of variability—some looked like the young group, some like the older group. This told us that the aging process that determines how you're going to fare at age 80 probably begins around age 40 or 50."

Reserving Space

Barring trauma or illness that would affect brain health, the ability of neurons to ramify remains strong throughout a person's life. One of the more captivating ongoing investigations of brain health began nearly 20 years ago with a pilot study that looked at healthy aging in residents of a retirement community of Catholic nuns. This largely closed community provided the researchers with a nearly ideal set of participants; the nuns had not only carefully preserved their personal and medical histories but they had also conformed to a documented lifestyle. In addition, the nuns agreed that, after their deaths, their brains would be donated to the study.

The investigators explored these precious donations in the hopes of isolating factors that affected the nuns' cognitive functioning. They found that cognitive capacity was compromised for women whose brains showed signs of cardiovascular disease, such as brain stroke. But they found cognitive function remained strong for women whose brains showed little to no evidence of cardiovascular trauma. Perhaps most interestingly, the researchers also found strong cognitive functioning among stroke-free women whose brains showed moderate to advanced Alzheimer's disease. Such brains, they speculated, drew upon reserves that delayed or offset the symptoms of dementia.

Cognitive reserve—the capacity to sustain brain function and to build effective networks that are less susceptible to disruption, including that which accompanies normal aging or even disease—is a growing concept among neuroscientists. While not exactly a 401(k) for your brain, cognitive reserve acquired from a life of active and sustained learning can keep the brain healthier, longer.

"Cognitive reserve is like strength training for your muscles," Fotuhi says. "When you are fit, you can sustain that fitness for a long period of time. There is compelling evidence that synaptic plasticity continues through age 70 and that brain volume can even increase among healthy adults, especially those who enjoy teasing their brains and exercising regularly. The idea that plasticity exists only in children is completely outdated."

Research on the molecular and physical changes that the brain undergoes with time will likely continue to overturn contemporary ideas of how age, disease, and lifestyle affect our ability to gain, maintain, and recall our individual library of memories. That our brains do alter with age is undeniable. But the lens of research increasingly shows us that when good overall health is maintained and brains are kept agile through learning and challenge, life—and memory—can remain rich for a long time. ■

Ann Marie Menting is associate editor of the Harvard Medical Alumni Bulletin.



WHAT TANGLED WEBS

People with Alzheimer's disease tend to weave modifications into their memories.

by ANDREW E. BUDSON

"Of course I pay my bills each month," my patient said, as the daughter sitting next to him shook her head. Later, while he was undergoing cognitive testing, she explained more fully: "That's the problem—he remembers doing things he hasn't done. When the electric company shut off his power, we found he hadn't paid any bills for about six months. He swears he paid them all. I worry whether he can keep living alone. He tells me he takes all his medications, but how do I know that's true?"

People with Alzheimer's disease not only fail to remember previously learned information, but they also experience distortions of memory and false memories. Distortions of memory may include simple but critical aspects of daily life. Alzheimer's patients may falsely remember, for example, that they have already turned off the stove or taken their medications, leading them to neglect these tasks.



method of creating false memories is to present a list of words—such as *candy, sour, sugar, bitter, taste, honey, heart,* and *cake*—that all relate to a theme word, which is not itself presented.

More dramatic distortions of memory occur when Alzheimer's patients substitute one person in a memory for another, combine two memories, or believe that a long-ago event occurred recently. These distortions may fall under the definition of confabulation—when people fill a gap in their memory with a fabrication they believe to be true.

Sometimes a false memory can be confused with a psychotic delusion or hallucination. A person may claim, for instance, to have recently seen and spoken with a long-deceased family member. Although visual hallucinations are part of Parkinson's disease dementia and dementia with Lewy bodies (dementias that are characterized by parkinsonism, visual hallucinations, and fluctuations), an Alzheimer's patient is usually more likely to suffer from a memory distortion or a false memory than a true auditory and visual hallucination. The same is true for patients who claim that someone has broken into their house and rearranged their belongings. That these symptoms likely represent false memories rather than true hallucinations or delusions has treatment implications, as false memories respond better to memory-improving medications than to antipsychotics.

My interest in memory distortions began with a simple clinical observation: most of my patients with memory problems triggered by mild Alzheimer's disease could not live alone, while most of my patients with memory problems stemming from encephalitis, temporal lobe epilepsy surgery, and other etiologies could live independently. It was clear that something other than simple memory loss was at work in those with Alzheimer's. My discussions with patients and their caregivers soon showed that false memories and memory distortions made the use of routines and reminders more difficult for Alzheimer's patients than for those with memory loss from other conditions.

Bearing False Witness

At Bedford Veterans Administration Hospital in Massachusetts, my colleagues and I began our research into memory distortions by creating false and distorted memories in healthy older adults and then determining whether Alzheimer's patients could use the same mechanisms that the healthy participants used to suppress these false memories. We created false memories by presenting healthy people with a list of words—such as *candy, sour, sugar, bitter, taste, honey, heart,* and *cake*—that related to a theme word, which was not itself presented. Study participants were highly likely to falsely remember on free-recall tests and falsely recognize on recognition memory tests the theme word—in this case, *sweet*. (Even healthy younger and older adults falsely recognize more than two-thirds of such theme words.)

One way to reduce false recognition in healthy individuals was simply to have them repeat the theme word several times. These repetitions helped them recall particular words, thus allowing them to resist the lure of the non-presented yet central theme word. In two studies, we found that repetition allowed healthy older adults to develop specific recollection of words on the list, which in turn reduced their rate of false recognition. Among Alzheimer's patients, however, repetition only helped them grasp the theme of the list, thus leading them to err more often in choosing the theme word, paradoxically *increasing* their false recognition rate.

Another way that healthy individuals reduced false recognition of related words was by pairing the words with pictures. Although this reduction could simply reflect the fact that pictures are better remembered than words, researchers at Harvard University have shown that false recognition decreases because the stories that form from picture–word pairings are more distinctive, and thus, more memorable.

The basic idea of this heuristic is that some events are so distinctive they would have to be memorable. If you were asked, "Have you killed a fly in your office within the past year?" you might find the answer elusive, because for most people killing a fly is neither remarkable nor distinctive. If instead the question was "Have you killed a snake in your office within the past year?" you would answer confidently, because the memory would have been distinct.

We investigated whether Alzheimer's patients could use this distinctiveness heuristic to reduce their false recognition rates. We experimentally determined that Alzheimer's patients *could* use the heuristic. Their poor memory, though, limited their ability to reduce their false recognition rate.

In Living Memory

Studying the frequency of memory distortions and false memories in the real world can be difficult. The terrorist attacks of September 11, 2001, though, provided us an opportunity. We contacted Alzheimer's patients and healthy older adults with a phone questionnaire within weeks of the attacks, again three to four months later, and finally one year afterward to evaluate both their memory of and emotions about that day.

Memory distortions were common among all participants, reminding us that a vivid memory isn't necessarily an accurate memory. Even healthy older adults showed a high rate of memory distortions—on average 25 percent—as they misremembered such details as where they were and whom they were with when they first heard of the attacks. Alzheimer's patients showed even less accuracy, with memory-distortion rates approaching 50 percent. In contrast, memory-failure rates—with study participants saying, "I don't know" or the equiv-



alent—were relatively low: 13 percent in the Alzheimer's patient group and only 1 percent in the healthy older adult group. Thus, when it comes to remembering personal information related to national traumatizing events, Alzheimer's patients and healthy older adults are more likely to misremember than to say "I don't know."

We recently conducted several laboratory studies that also have real-world significance. In one of these studies, we first presented Alzheimer's patients and older adult controls with sentences that could be either true or false, followed by a label of *true* or *false*. For example, "In New York City, the 53rd Street bus will take you uptown: *false*," or "It takes 32 coffee beans to make a cup of espresso: *true*." Interestingly, although the Alzheimer's patients correctly remembered that 69 percent of the true statements were true, the same patients incorrectly remembered that 59 percent of the false statements were true. This finding suggests that if you tell someone with mild Alzheimer's disease that something is false, they are *more* likely to remember that it's true. The statement, "The 53rd Street bus won't take you to your sister's house, so take the 67th Street bus instead," for example, will lead an Alzheimer's patient to be more likely to falsely remember that the 53rd Street bus *is* the correct bus than if the 53rd Street bus had not been mentioned at all. This finding has significant relevance for clinicians and caregivers who need to communicate with Alzheimer's patients.

Brain Storming

To begin to unravel the underlying pathophysiology of these memory distortions in Alzheimer's patients, we elected to test the role that frontal-lobe pathology may play in the disease. We began by examining false recognition in patients with frontal-lobe lesions caused by stroke or tumor resection. We gave these patients and matched control subjects the same related-word lists we had given Alzheimer's patients and found that patients with frontal lesions showed even higher levels of false recognition than the Alzheimer's patients did.

Some of our newer research investigates how the brain forms and retrieves memories. In this work, we use 128 channels of EEG to produce a particular type of neural activity as subjects are shown a picture or presented with a previously studied word. We found that when we average the EEG across 30 or so trials, we can see—in real time—the electrical activity associated with retrieving a memory. These studies have shown that, compared with healthy older adults, people with mild Alzheimer's disease exhibit vastly reduced frontal-lobe activity, thus providing support to the hypothesis that frontal-lobe dysfunction may cause the high levels of memory distortions in people with mild Alzheimer's disease.

An improved understanding of the causes of false memories and memory distortions may lead to behavioral and pharmacological treatments that can decrease their effects. Reducing the effects of these tangled memories may in turn allow patients with Alzheimer's disease to live fuller, more independent lives. ■

Andrew E. Budson '92 is director of the Center for Translational Cognitive Neuroscience and the Geriatric Research Education Clinical Center at Bedford Veterans Administration Hospital in Bedford, Massachusetts. He is also director of cognitive neuroscience research at the Alzheimer's Disease Center at Boston University School of Medicine and a consultant neurologist in the Division of Cognitive and Behavioral Neurology at Brigham and Women's Hospital in Boston, Massachusetts.



What happens when memories are too painful to bear?

by JESSICA CERRETANI

PERISH THE THOUGHT

IN THE FILM *ETERNAL SUNSHINE OF THE Spotless Mind*, a man visits a doctor who offers him an unusual solution to coping with his painful breakup: targeted memory erasure, a procedure guaranteed to wipe out all recollection of his failed relationship. Fiction, to be sure, but research currently taking place at Massachusetts General Hospital may someday help cement medicine's ability to dull—although not completely eliminate—certain traumatic memories.

Forgetfulness isn't usually something we welcome. People with post-traumatic stress disorder (PTSD), however, can find persistent memories of past trauma so overwhelming that they have difficulty functioning in the present. For these people, says Roger Pitman, an HMS professor of psychiatry and director of the PTSD Psychophysiology Laboratory at MGH, weakening selected memories may be just what the doctor ordered.

Once called battle fatigue and shell shock, PTSD is now considered an anxiety disorder that can develop not just in combat veterans, but also in survivors of rape, childhood abuse, car accidents, and other traumatizing occurrences. These memories are easy to acquire: Most of us can recall where we were and what we were doing on September 11, 2001, far more vividly than the events of September 10, 2001. The challenge, Pitman says, is how to tame seemingly indelible traumatic memories.

The answers to this puzzle may lie within the brain itself. Research suggests neurotransmitters released from the brainstem during stress play a key role in emotional memory. People with PTSD have been found to have lower-than-normal levels of cortisol and higher-than-average levels of noradrenaline, a ratio that may enhance learning and memory. This chemical pattern appears to improve the transfer of traumatic events from short-term into long-term memories, a process known as consolidation.

In people with PTSD, says Pitman, "the emotional arousal and biological and neurological changes that accompany trauma may burn

memories of the event into the brain so deeply that they keep coming back." When traumatic memories resurface—triggered by a sound, smell, or other stimulus associated with the initial event—they may create additional biochemical changes that engrave them in the brain more deeply. This recall and repetition of the original memory is called reconsolidation. It, in turn, may lead to a greater likelihood the memories will resurface.

This biochemical process may help explain why even the most successful therapeutic approach to PTSD—cognitive behavioral therapy—yields lasting symptomatic improvement in only about half of those who receive it. Researchers elsewhere have conducted experiments designed to quell PTSD at the cellular level in rats. Consolidation builds—and reconsolidation maintains—connections between neurons that are mediated by a protein. In an attempt to prevent reconsolidation, researchers injected stressed rats with anisomycin, a drug that inhibits the synthesis of this protein. Rats given anisomycin after trauma showed less fear when exposed to stimuli.

Pitman's laboratory has been studying how pharmaceuticals affect memory consolidation and reconsolidation in humans. In one noteworthy trial, Pitman and his colleagues gave the beta-blocker propranolol to 18 people who arrived at an emergency department following a trauma. The anti-adrenaline drug replaced anisomycin, which is too toxic for human use. "There's evidence that a certain level of adrenergic activity is required for memories to be consolidated," explains Pitman. "Because propranolol can block adrenergic activity, it might also interfere with memory consolidation."

The results were stunning: The treatment group received just a ten-day course of propranolol, beginning within six hours of the traumatizing event. Three months later, participants listened to audiotapes in which they described their initial trauma. People with PTSD typically have strong psychophysiological responses during this procedure: sweating, muscle twitches, accelerated heart rate. Yet subjects who had received propranolol didn't show such physiological responses, compared with 23 controls. "From that," says Pitman, "we inferred that their traumatic memories had been weakened."

His team's findings made headlines, with reports trumpeting the promise of an effective new PTSD treatment. But critics expressed alarm that obliterating memories might prevent people from working through trauma and, worse, eliminate what it means to be human.

Such concerns, suggests Pitman, are premature. His findings didn't show that traumatic memories had been erased altogether, but rather dulled. "We have yet to encounter a person to whom we've given propranolol who says, 'I don't remember the trauma at all anymore,'" he says. And despite the Hollywood comparisons, none of his subjects' other memories are erased. "People wonder what would occur if they were in our lab talking about their trauma and they thought about their dog," he says. "Would they end up forgetting their dog? We don't have nearly that power."

In fact, Pitman stresses that his results, while promising, are preliminary. He hopes to further our knowledge with additional research. His team recently received a large grant from the U.S. Department of Defense to investigate about a dozen drugs with the potential to inhibit memory reconsolidation in animals and humans. If the research is successful, says Pitman, such pharmaceuticals "may someday provide an alternate and potentially more efficacious way of treating PTSD." ■

Jessica Cerretani is assistant editor of the Harvard Medical Alumni Bulletin.

Probing False Memories

The image of little green men spiriting away victims to a spaceship for a battery of unpleasant tests is a scene out of science fiction. But for some people, "memories" of alien abduction feel all too real, says Roger Pitman, director of the PTSD Psychophysiology Laboratory at Massachusetts General Hospital, who has studied how the belief of trauma relates to symptoms of post-traumatic stress disorder.

The physical responses of people with established PTSD—sweaty palms and a racing heart, for example—have been cited by some as "proof" of the veracity of recovered memories in people who experience similar symptoms. Working on a team led by Richard McNally, a Harvard psychology professor, Pitman and others challenged the significance of these reactions by testing the physiology of people with false memories. Because it's difficult to authenticate most recovered memories, such as those of childhood abuse, researchers chose a memory they suspected to be untrue: that of alien abduction. Evidence suggests that people who claim to have been abducted by aliens have instead experienced sleep paralysis, in which a person awakens during REM sleep to temporary muscle paralysis and hallucinations.

McNally, Pitman, and their colleagues looked at ten people who believed they had been abducted by aliens. The subjects described their alleged alien encounters; their stories were recorded and later played back to them while researchers monitored their heart rate and other indicators of stress. The team's findings came as a surprise: People who claimed to have been abducted exhibited stronger psychophysiological reactions to the abduction recordings than they did to positive and neutral recordings, compared with 12 controls. These responses were similar to those that occur in people with established PTSD when they recall traumatizing events.

The results aren't proof of alien abduction, Pitman says. Rather, the feelings of fear and helplessness that can accompany sleep paralysis may help explain the subjects' reactions. "A strong physiological response during sleep paralysis may consolidate the memory of what the person was imagining at that time," he explains, "even though that memory is false." ■

IMAGES ON FACING PAGE: ANTHONY HARVIE/PHOTOGRAPHER'S CHOICE RF/GETTY IMAGES (NOTEPAD) AND BRIAN LAUFENBERG/ISTOCKPHOTO.COM (BRAIN)

Harvard Medical
ALUMNI BULLETIN

presents

A USEFUL {YET SLIGHTLY IRREVERENT}



GUIDE TO MEMORY PRESERVATION



memory upgrade

Despite a wealth of brain boosters on the market, a psychiatrist remains a frugal shopper. *by* ELISSA ELY

WHENEVER I VISIT MY DOCTOR, after we have finished with the usual blood-pressure and weight-loss scripts, I ask him what he's doing to keep his mind sharp. Inquiring on this topic is like asking someone to show a couple of snapshots from his last vacation. The rest of the world then waits for as long as it takes.

Dr. Q., my specialist, has a desk littered with pill bottles. He pops supplements between patient appointments, one to two dozen pills a day, but the particulars change each time we meet. The most recent combination (as far as I can recall) included high-dose fish oil, several amino acids, coenzyme Q10, thyroid hormone, testosterone, and vitamins C and D. He is off vitamin E and beta-carotene, disappointed in ginkgo, and reconsidering Zocor since he read a study linking statins to memory loss. He lifts weights and carries index cards with facts he commits to memory. To improve praxis, he

ILLUSTRATIONS FOR THIS ARTICLE RYAN SNOOK

In 2007, more than $225 million was spent as My Brain Trainer and Mind Spa. down additional neural pathways.

likes to draw his patients' blood himself in the office. He is a marvel.

After each consultation, I rush home, take out my seven-day pill dispenser (fastidiously packed with my own supplements) and stir the contents with a forefinger. Royal jelly goes out, curcumin powder goes in. The recipe for a perfect brain is always in flux.

But I don't really need my doctor for this advice—there are dozens of other doctors out there willing to give it, in lists with such decisive titles as "Eight Essential Strategies for Keeping Your Mind Sharp and Body Young," "Nine Strategies to Improve Memory," and "Ten Steps to Better Memory in Your Seventies." Each author is dead sure. But you see the dimensions of the problem already: no one can agree on a number.

One could begin with "smart drugs." They may enhance cognition, and pharmaceutical companies are sprouting up everywhere to compete for them. It's like an *Iron Chef* smackdown, with contestants grabbing dishes from the hot stove and racing them to the patent office for judges to taste.

Smart drugs are supposed to increase brain metabolism, improve cerebral circulation, and quash free radicals. There are calcium-channel modulators, nicotinic-receptor partial agonists, pyrrolidone derivatives. Don't forget the "building blocks of life"—the amino acids, especially tyrosine and phenylalanine. We can take lecithin and L-carnitine, inositol, vasopressin, and lipid-lowering statins. The selective serotonin-reuptake inhibitors may cause hippocampal neurogenesis—though they also cause frontal apathy, or "Prozac poopout."

Years ago, a nurse in a hospital where I used to work ran a thriving underground business in grape pip extract. Now you can buy it online, purified and ten times as costly. For those who can't swallow pills, the aroma of peppermint has been shown to improve performance on a Cognitive Research Computerized Assessment Battery.

Dietary factors are earthier than nootropics, and you don't have to order them from specialty stores. The well-stocked pantry carries everything. You've got your fruits and vegetables, your whole grains, your omega-3s. Red wine with resveratrol is recommended nightly. Take one to two glasses, but not more; this could qualify as alcohol abuse—which would damage the very memory you're trying to preserve.

Then there are the many varieties of exercise. Physical exercise, of course, has been popular since the Socratic academy. It is cheap and healthful, with only a few caveats, such as avoid football, boxing, and skiing without a helmet. Aerobics are supposed to increase brain-derived neurotrophic factor and hippocampal neurogenesis and to decrease prefrontal shrinkage. The devil lurks in the details, though. Panting nonathletes, checking their pedometers, want to know: exactly how many laps, how many sets, how many summits? Here experts are back to their disagreeing numbers—half an hour, three times a week; sixty minutes, six times a week; daily, for as long as you can bear. This much is vaguely clear: more is likely better.

Social exercise may be effective, too. In one study, ten minutes of pleasant personal interaction each day increased Mini-Mental State Exam scores as much as the same amount of intellectual study. I find this heartening. It speaks well of our species to think that a dozen friends are worth a dozen logic problems.

There is also exercise for the brain itself: In 2007, more than $225 million was spent by the hopeful and the despairing on brain-fitness software such as My Brain Trainer and Mind Spa. The theory is that math, logic, and memorization problems lay down additional neural pathways. Six months after enrolling in one memory enhancement program, a group of 60- to 90-year-olds without dementia tested no better than their non-enrolled peers. But they were much less worried about themselves, which is worth the price of admission. Some of us will always prefer friends to brain exercises, but that is a matter of taste. I won't denigrate computer games if you respect the gossip I live for.

If you are inclined to invasive techniques—fatty-cheek–pad implants instead of moisturizer—there is deep brain stimulation. If you are less inclined, there is poetry. Alliteration and repetitive consonant sounds cause easier retrieval of similar sounding phrases. So do mnemonics, associations, and chunking information into smaller categories. Greek orators memorized long speeches by visualizing them-

by the hopeful and the despairing on brain-fitness software such
The theory is that math, logic, and memorization problems lay



selves walking a familiar road, linking sequential landmarks with sequential points they wanted to make. Recall was as simple as a mental walk home.

Finally, for those who prefer no effort, there is the absence of exercise altogether. Ninety-minute daytime naps have been found to increase long-term memory consolidation. Unfortunately, they also make it harder to sleep at night, which will decrease long-term memory consolidation. On this topic, there is no god.

To what end all these efforts? What comes from supplemental, nutritional, aerobic, neurosurgical, Grecian, sociable, slow-wave strategies? Not better memory, at least not in a simple way. First of all, the brain is more complicated than our efforts to master it; there are a multitude of memories to worry about losing. We need short-term working memory, but we also need long-term declarative and procedural memory. Second, the act of remembering follows several stages: acquisition, consolidation, and retrieval. Each memory type and each stage is differentially sensitive to age and insult. Therefore one fix cannot fix all. You need to spend the rest of your life in repair.

When my doctor and I are sitting across his pill-addled desk, there is a question I have never brought up. It may be too plaintive for a specialist. Why do we take memory to be the most important measurement of human worth? It's as if we judge the value of our minds to be the sum value of our selves, and no other measurements count. Dementia is tragic, but there is more to people than acquisition, consolidation, and retrieval. In my dotage—when I may no longer be able to learn what I should, and when I cannot recall what I want to—this is what I hope for: that someone I love will lead me by the hand to a place outdoors with flowing water and a waiting dog. We will sit together, listen to the water, and stroke the dog. In that place, I like to think, we will be happy—whether we remember it or not. ■

Elissa Ely '88 is a psychiatrist at the Massachusetts Mental Health Center.

think nothing of it

One prescription for keeping the brain active may be quite



simple: meditate. *by* JESSICA CERRETANI

DOING CROSSWORDS, LEARNING A LANGUAGE, AND engaging in stimulating conversations may all help preserve brain function. But research suggests an intriguing—and seemingly contrary—approach to memory enhancement: thinking about *nothing*. That's the finding of Sara Lazar, an HMS instructor in psychiatry, and her colleagues at Massachusetts General Hospital. Their research suggests that regular meditation may change brain structure in positive ways.

It's clear that meditation—a concentrated focus on the present moment—can increase relaxation. But its benefits may not end there. "Meditation appears to have profound effects on attention and emotion," says Lazar, who has practiced meditation for more than a decade. "It can color the entire way one sees the world." A growing body of evidence supports this claim, showing links between regular meditation and increased empathy, attention, and focus.

Such changes, Lazar's team posited, should be evident in the physiology of meditators. "We suspected that meditation alters the very way the brain is wired," she says. To investigate, they recruited 20 men and women who regularly practiced Insight meditation, a technique that employs mindfulness, the nonjudgmental awareness of the present. While previous studies have centered on Buddhist monks, who meditate for hours at a time, Lazar's subjects were everyday people. They practiced an average of 40 minutes of meditation—in this case, paying attention to their breathing and physical sensations without trying to change them—on most days of the week.

Using magnetic resonance imaging, the researchers compared brain scans of the meditators to those of non-meditating matched controls. They found that brain regions associated with attention, interoception, and sensory processing—namely, the prefrontal cortex and right anterior insula—were thicker in subjects who meditated than in those who didn't.

The study, published in *NeuroReport* several years ago, confirmed what Lazar already suspected: When it comes to the brain, she says, "it isn't just 'use it or lose it,' it's 'use it—and it grows.'" Previous studies have shown that other types of regular practice, such as learning to juggle or playing a musical instrument, are also associated with increased brain volume. Much the way physical exercise builds muscles, so too does mental training help shape the brain.

The significance of this brain growth is still unclear but may have implications for memory preservation, says Lazar, whose team is currently conducting a cross-sectional study of meditators with increased cortical thickness to determine how they fare in tests of memory and attention. A longitudinal study, in which subjects' brains will be examined both before and after learning to meditate, is also in the works.

The potential value of meditation may be greatest for age-related memory loss: Lazar points out that increased prefrontal cortical thickness was most pronounced in older study subjects. "The 50-year-olds who meditated had the same thickness as the 20- to 30-year-old meditators and controls," she explains. "That suggests regular meditation may slow rates of the cortical degeneration that comes with age."

Whether that means doctors' new mantra should be, "Meditate for 40 minutes and call me in the morning" remains to be seen. So does the effect of other types of meditation and yoga on brain structure, although Lazar believes they may have similar benefits. What is certain is that meditation has officially made the leap from the province of yogis, monks, and New Age enthusiasts to the research laboratory—with promising results. That's worth our attention. ■

Jessica Cerretani is assistant editor of the Harvard Medical Alumni Bulletin.



EYEGLASS
SEDATE
FLORIDA

Memory Splat Mat

by ALICE FLAHERTY

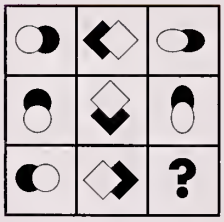
WHEN TO TAKE THIS TEST: People who eat breakfast score higher on memory tests than those who skip the morning meal, so what better time to test your wits?

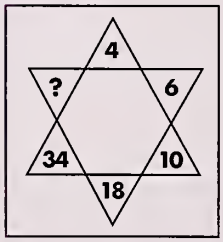
WHAT THIS TEST DOES: Tells you which of the three Ds is causing your poor memory: dementia, depression, or . . . congenitally low IQ. Anxiety can be lumped with depression.

WHAT YOU NEED: Your napkin and a pencil for recording answers. Don't write on this splat mat, because if you really have lost your memory, you'll want to refer to the mat again and again.

Before you begin, look at the three words in the coffee stain to the left for five seconds. Then cover them with your cereal bowl and take the rest of the test.

1. How old are you?
2. In 60 seconds, name all the animals you can think of.
3. Name the object in each of the pictures to the right.
4. What do those pictures have in common?
5. Define ibis, ibex, and imbroglio.
6. Who notices your memory lapses more often—you, or others, such as your spouse or boss?
7. Name the seven dwarfs in Disney's *Snow White and the Seven Dwarfs.* (Skip this question if you weren't born in the United States.)
8. Do you have more trouble starting projects than you did three years ago?
9. Have you recently lost interest in things you used to enjoy, such as sex or television?
10. Does a word you were groping for come back spontaneously later?
11. Remember this: "Frank Jones's feet were so big, he had to put his pants on over his head."
12. Without moving your cereal bowl, write down the three words that it covers.
13. Do you have more trouble making decisions than you did three years ago?
14. Complete the pattern in each series in the two figures to the left.





Alice Flaherty '94, PhD, is an HMS assistant professor of neurology at Massachusetts General Hospital.



ANSWERS

A. The Theory Behind It All

People with dementia are less aware than others that their memory is impoired—and worry less about it. Depression and anxiety couse more trouble with memory recall thon with encoding, so memory problems provide good diognostic clues for both. Memory loss from depression stems from diversion of ottentional resources to managing the illness. It *is* reversible.

B. Scoring

Points ore divided into three cotegories:
B = boseline low intelligence; D = depressed; S = senile

1. Age: 1 D point if younger thon 55,1 S point if you're not sure.
2. Verbol fluency: If fewer than six onimols, 2 S points; if between six and twelve onimals, 1 S point.
3. Wig, worm, wheelchair. 1 S point for eoch error.
4. Their names all start with "w." If your first thought wos thot they all have to do with aging and death, get 1 D point.
5. Roughly, a bird, a gazelle, a mess. If you didn't have ony idea obout ony of them, get 1 B point. Word recognition is preserved in early dementia.
6. If you notice ond worry more obout your lapses, 1 D point. If others do, 1 S point. Most people who ore onxious obout their memory do not hove dementia.
7. Hoppy, Grumpy, Sleepy, Sneezy, Boshful, Doc, ond Dopey. If you nomed fewer thon 3, get 1 S point. Sleozy wos not o dworf.
8. If yes, 1 D point. People with mild dementio con stort projects unless they're olso opothetic; then they don't notice onywoy.
9. If yes, 1 D point.
10. If yes, 1 D point.
11. The story wos "Fronk Jones's feet were so big, he hod to put his ponts on over his heod." Forgetting the nome is fine. If you didn't remember the story ot oll, 1 S point. If you didn't understond why it wos funny, 1 B point. If you understond why someone like me might think it was funny, but you didn't hove even the tiniest urge to laugh, 1 D point.
12. If you completely blonked on one, try these prompts: (1) related to vision; (2) means colm, sort of; (3) a state. Now check the onswers. If you forgot one or more, but remembered with o prompt, 1 D point. If the prompts didn't help, 1 S point.
13. If yes, 1 D point.
14. Stor = 66; grid = ◐◯. For each error, 1 B point.

C. More Scoring

1. If you keep hoving to look bock to remind yourself whot B, D, ond S stond for, thot's bod but non-specific—odd o point to oll three cotegories.
2. Write your scores here: B____ D____ S____. If you see other scores olready there, ond they look like they're in your hondwriting, add one S point—you've forgotten you took the test already.
3. If your S score is greater than 4, you'll be tempted to do memory-enhancing puzzles such os crosswords. But it turns out that normol sociol interoction, especially gossip, broodly stimulotes cognition os much as—or perhops more thon—Sudoku and word-find puzzles con.
4. If your D score is greater than 4, see a doctor. Remember that "appropriate" depression or onxiety is still depression or anxiety, still weighs you down, and is treotoble.

D. Questions that Don't Appear on the Exam

1. Do you forget people's names? Everyone forgets nomes. The humon broin evolved in Neolithic communities thot tended to include fewer thon 150 people. Now, how does that compare with the number of people in your address book? You do the moth.
2. Do you forget where you left your keys? Sure, it's bad, but it's very nonspecific. The most common couse of forgetting your keys is that you hove something more importont to worry obout. Highly successful people forget them all the time; that's why they hove personol assistants.
3. How reliable is this test? It's opproximotely 60 percent more reliable than those *Cosmo* test-your-sex-quotient quizzes.

PHOTOS FURNALD/GRAY (BREAKFAST MONTAGE); GETTY IMAGES (WORM, WIG, WHEELCHAIR)

Mind Games

When it comes to building a better brain, sometimes play's the thing. *by* MAJID FOTUHI

CHILDREN LEARN THROUGH PLAY, whether by stacking building blocks or indulging in make-believe. But imagination, recreation, and discovery needn't be relegated to the schoolyard. A growing body of research suggests that people of all ages can tone and enlarge their brains through play, enhancing their memories and staving off the eroding effects of aging on the brain.

Word games are a fun—and effective—way to challenge your brain. In one study, for example, a team of researchers at the Columbia University College of Physicians and Surgeons discovered that elderly people who engaged in brain-stimulating activities such as crossword puzzles remained sharper for a longer time than those who didn't.



In fact, improving your vocabulary and memorizing passages from books are among the easiest and most efficient ways to enhance your brainpower. Memorizing a page of poetry, like solving puzzles, stimulates both the temporal and the frontal lobes. And researchers believe that if you challenge your brain by learning a new language, new synapses form, thus helping tone the very parts of your brain that can wither with age.

The games needn't be word oriented. Just as physical exercise builds muscles, learning and practicing new skills provides a neural workout that helps bulk up the brain. Neuroscientists at the University of Hamburg in Germany studied the brain images of a group of adults before and after they were taught how to juggle. After three months, the jugglers' brains had increased in size in the area used for hand-eye coordination and motor activity—the occipitotemporal cortex.

Playing music has similar effects. If you had never studied music and were to begin playing the piano today and practiced every day, the parts of your brain attuned to music appreciation and hand movement would develop and mature. As you struggled to play the correct notes, you would create new synapses. And after just a few months of regular practice, the difference in the size of the areas of your cortex linked with appreciating and learning music, such as the right frontal lobe, would be noticeable on an MRI scan.

Physical play itself can boost brainpower, particularly if it involves learning and memorizing a sequence of movements, such as sports maneuvers, dance steps, and tai chi poses. The very act of exercise increases hippocampal levels of brain-derived neurotrophic factor, a protein that improves neuron health and helps synthesize more synapses. Playing with others—whether team sports or board games—involves social interaction, which is also linked with better memory.

And don't forget to employ games as memory devices: Use your imagination to memorize lists, make associations, and create mnemonics. Medicine is filled with mnemonics. To remember the superior thyroid artery branches, for example—muscular, infrahyoid, superior laryngeal, sternomastoid, cricothyroid, and glandular—some doctors simply recall May I Softly Squeeze Charlie's Girl?

So remember this: When it comes to preserving memory, kidding around can help you play for keeps. ■

Majid Fotuhi '97, PhD, is an assistant professor of neurology at the Johns Hopkins University School of Medicine, director of the Center for Memory and Brain Health at Sinai Hospital's LifeBridge Health Brain & Spine Institute, and a clinical instructor in neurology at Harvard Medical School. His most recent book is The New York Times Crosswords to Keep Your Brain Young: The 6-Step Age-Defying Program *(St. Martin's Press, 2008). The "Brain Quiz" crossword puzzle is reprinted from Fotuhi's book with permission. The author of the puzzle, Michael Shteyman, is a student at the University of Maryland School of Medicine.*

Brain Quiz *by* Michael Shteyman

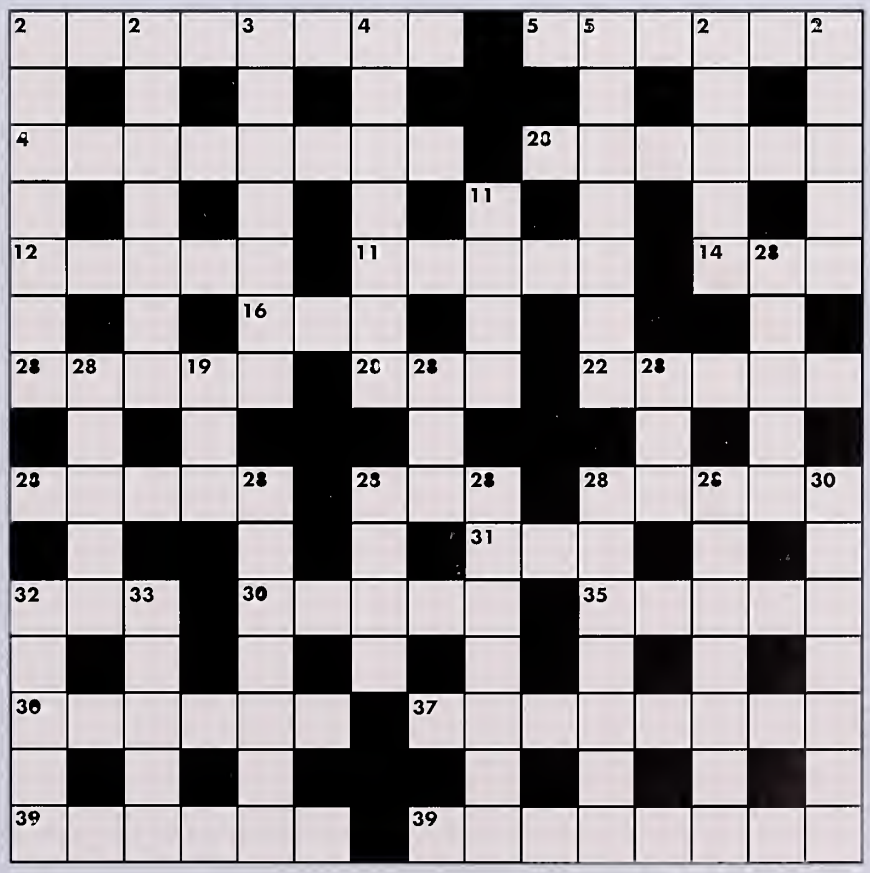
ACROSS

1 Stay positive and show a lot of 37-Across (2 wds.)
5 Endorphin, released during exercise, can be classified as this type of compound
9 Leptin will not be able to do its job if this link stops working (2 wds.)
10 Entered (2 wds.)
12 Prefix after milli-, nano-, and pica-
13 Live and breathe
14 One reason for the buildup of amyloid plaques in the brain
16 Teachers' org.
17 Opposite of "relaxed"
20 Affected by unhappiness, as a person with depression
22 Chocolate, ice ___, and candy (foods you shouldn't eat every day)
24 Rub out, as text
26 Physicians' degs.
28 Beginning
31 Yang's counterpart
32 Chemical formula for water, spelled out letter by letter
34 Vegetable with antioxidant and anti-inflammatory properties
35 Sleep disorder that deprives the brain of oxygen
36 Hemoglobin deficiency that can contribute to memory problems
37 Positive outlook on life that can help prolong the health of your hippocampus
38 Finis (2 wds.)
39 ___ leg syndrome (disorder that can interfere with your ability to sleep well)

DOWN

1 Kind of diet that can raise your risk of a heart attack (2 wds.)
2 ___ E, antioxidant compound implicated in better brain function in the elderly
3 Cortisol, adrenaline, or leptin
4 Railroad worker Gage with frontal lobe damage
6 "Old dogs" can learn new tricks because the brain is flexible and ___
7 DHA is an example of ___-3 fatty acid, the best food for the brain
8 What you should do to improve your hand, eye, and foot coordination
11 Meditation is one way to distract it from your daily thoughts
15 Purple fruit rich in antioxidants that help fight inflammation
18 Planet between Venus and Mars
19 Captain's cry for help
21 Assistance
23 What you can do to increase the levels of brain-derived neurotrophic factor, or BDNF, in your brain
25 Limbic lobe is responsible for its production
26 Certain brain scans, for short
27 Contact point between brain cells
28 Trying to lose weight (3 wds.)
29 Early morning phenomenon
30 Emotional or physical injuries that can play a role in memory problems
32 Anxiety and stress can affect this organ in your body
33 Overweight, as people with a higher risk of hypertension and Alzheimer's disease

The answers can be found at http://alumnibulletin.med.harvard.edu/bulletin/autumn2008/solution.php




DREAM WEAVER

The best advice for optimal memory? Sleep on it.

by Jessica Cerretani

HE WAS CLIMBING THE mountain again. He could feel his feet navigating the craggy outcroppings, his hands gripping the rocks. But Robert Stickgold, a sleep researcher and an associate professor of psychiatry at HMS, wasn't on Camel's Hump; he had reached the summit of the Vermont peak earlier that day. He was asleep in bed—but the memory of his trek wouldn't fade. Even when he awoke during the night and went back to sleep, "I still found myself dreaming of the climb," he says. "I had the profound sense that this was somehow important."

Perhaps, he mused, those recurring images and sensations were his brain's attempt to help his body remember how to traverse the mountain. When he returned to Boston, Stickgold shared his suspicion with his students: that sleep-onset, or hypnagogic, dreams—the thoughts and images that run through our minds just as we fall asleep—play an important role in memory and learning.

Studying the idea, however, posed a challenge. Stickgold knew he couldn't just take a group of subjects mountain climbing. His students suggested a simpler—and safer—solution: Tetris, an addictive computer game that involves the repeated positioning of falling shapes into flush lines. Those who had played the game often remembered dreaming about it later.

In the study that ensued, 27 participants played Tetris on and off for three days. Stickgold's team then monitored their hypnagogic dreams. All of those who recalled their dreams reported seeing the same falling Tetris shapes. They also improved their Tetris-playing skills over the course of the study. Yet the findings, published nearly a decade ago, remain significant not only for showing what dreams the subjects had, but *who* had them. Five amnesiacs had been included in the study, mostly as a nod to a student who wanted to research amnesia but couldn't obtain funding. Surprisingly, three of the five also reported dreaming of falling shapes. And while the amnesiacs didn't improve as much as the other subjects, at least one knew which computer keys to press—even though she couldn't recall ever having played the game. "This," says Stickgold, "suggests that the



Without a full night's sleep, memory, attention, focus, judgment, reaction time, and learning all suffer.

hippocampus, which is damaged in amnesiacs, isn't the part of the brain being used to construct hypnagogic dreams."

It may also explain why hypnagogic dreams aren't just episodic memories, which are controlled by the hippocampus. If they were, subjects would remember more details of the original experience, such as the room in which they played Tetris. The fact that they don't dream about these details suggests what Stickgold calls "a brilliant evolutionary gimmick": Our brains pinpoint the most important information—repetitive activities such as positioning the falling shapes or climbing the mountain—and discard the rest. "It may be that sleep has evolved to extract meaning and improve learning," explains Stickgold. "That's why dreams are always meaningful, even when they seem silly to us."

Dreams that occur during deeper, rapid eye movement (REM) sleep also have something to teach us, although the lessons may be less obvious. Imagine you're driving through an intersection and another car runs a red light. There's no collision, but it's a close call. That night, you dream you're playing bumper cars with your son and you're feeling unhappy. The message from your brain, says Stickgold, isn't that you hate amusement parks, but that you should be more vigilant behind the wheel. Because the hippocampus is not involved in REM sleep, the brain is unable to access episodic memories during this phase. The resulting dreams, while seemingly bizarre, still serve as warnings and lessons. "The real purpose of the relationship between memory and sleep," he says, "may be to inform us not about our past but about our future."

Stickgold's team continues to investigate that relationship. One study involves playing a recording of related words—such as *bed*, *night*, and *snooze*—for subjects, then testing them later on their recall. The word subjects tend to remember most—*sleep*—isn't even on the list. The implication, he says, is that our brains fill in gaps to retain the gist of something important, particularly after a night's sleep.

Other research by Stickgold's team suggests that the brain requires three stages for optimal memory recall—and that adequate sleep is integral to this process. During the first stage, the brain forms a memory, a phase that depends on about six waking hours to occur. If we nod off too soon, we lose that memory. For the second stage, we need at least several hours of shuteye to edit memories and sharpen learning. In the third stage, edited memories become stabilized and enhanced, allowing the brain to perfect previously learned skills.

Perhaps one of the more intriguing areas of research on Stickgold's agenda is the link between sleep disturbances and mental health. "Every major psychiatric disorder has sleep disturbance as one of its characteristics—and it's assumed that mental illness causes these disturbances," he says. "But I believe the relationship is at least bidirectional." He points to a study he's published that found schizophrenics who learn a simple task appear to show no overnight improvement in that skill, a possible sign that they may not process memories properly during sleep. Stickgold hopes to someday discover what function sleep and its effects on memory and learning may have in conditions such as depression, bipolar disorder, and attention deficit hyperactivity disorder.

So how much sleep do we need for optimal memory? "Simply put, we just don't know," Stickgold says. Some studies have found a 90-minute afternoon nap to be more effective than six hours of nighttime sleep at improving learning; other research suggests that consistency over time may be more important than the amount of sleep we get on any given night. One thing is clear: Sleep is necessary for optimal brainpower. Without a full night's sleep, memory, attention, focus, judgment, reaction time, and learning all suffer. Studies by Charles Czeisler, the Baldino Professor of Sleep Medicine at HMS, have graphically illustrated those consequences in medical residents: fatigue-related medical errors, needle sticks, and motor vehicle crashes.

Shuteye has other benefits, too. There's evidence linking sleep deprivation to decreased immunity and weight gain. The bottom line, says Stickgold, is that some amount of sleep is essential for good health. "The most depressing thing," he laughs, "is that I'm spending my entire career proving that my mother was right—about sleep, anyway." ■

Jessica Cerretani is assistant editor of the Harvard Medical Alumni Bulletin.



Recall Buttons

Combat retention deficit disorder with these tips. *by* AARON P. NELSON

EVEN MEMORY EXPERTS CAN BE FORGETFUL. MY WIFE AND I, BOTH neuropsychologists at Harvard-affiliated hospitals, once drove 50 miles before realizing we had neglected to pack our six-year-old daughter's security blanket. Rather than face a week of her despair, we returned home. And there, in our driveway, we found our other car with the key left in the ignition—and the engine running.

An old Chinese proverb tells us that the palest ink is better than the strongest memory. Although memory glitches may plague us all, we can still take steps to boost our powers of recall. Here are a dozen steps I prescribe to my patients—and try to follow myself.

Get Moving

Research shows that people who engage in regular exercise tend to stay mentally sharp into their eighties and beyond. Led by Eric Larson '73, a team of investigators at the University of Washington found, for example, that people aged 65 or older who exercised three or more times a week had a lower risk of dementia than their less active counterparts.

Exercise aids memory in several ways: It strengthens the lungs and the cardiovascular system, a combination that helps ensure the steady delivery of oxygen to the brain. Physical activity helps minimize the risk of diabetes, high cholesterol, high blood pressure, and stroke—all diseases that can impair cognition. Exercise may also increase connections between brain cells and enhance neurotransmitter function. For good brain health, engage in at least half an hour of moderately vigorous exercise most days of the week.

Stay Mentally Engaged

Your mind thrives on new challenges and learning experiences. In the MacArthur Foundation Study of Aging in America, researchers found that the characteristic most strongly linked with good mental functioning was level of education: Experts suspect that school-based education fosters a lifelong habit of learning. And education in the broader sense, outside classroom walls, builds cognitive reserve, or the resilience of the brain to withstand neuropathological assault.

Exercising your brain with challenging activities is believed to stimulate communication between brain cells. Some of these activities are obvious, such as doing crossword puzzles, playing chess, reading, and taking classes. But mental stimulation can also come from any deviation from your daily routine that makes you think, such as taking an alternative route while driving. Try to develop new skills—or relearn old ones you may have set aside; that trumpet stowed in your closet may be a good place to start.

Don't Smoke

In studies of memory and cognitive function, smokers perform worse than nonsmokers. It's unclear whether smoking directly muddles memory or is associated with memory loss because it causes illnesses that compromise brain function. It *is* clear, however, that smoking increases the risk of stroke and hypertension, two conditions that impair memory. Regardless of the exact link, if you smoke, it's never too late to quit: People who stop smoking show less cognitive decline than those who continue.

Drink Only in Moderation

While moderate consumption of alcohol may reduce the risk of dementia, excessive consumption is toxic to neurons. It is also a leading risk factor for Korsakoff's syndrome, a disorder that causes irreversible memory loss. If you are a heavy drinker, cutting back can prevent further memory loss and will usually lead to the recovery of some memory function.

Eat a Healthful Diet

A diet rich in fruits and vegetables, whole grains, and healthy fats from fish and nuts is vital to maintaining brain health. Many fruits and vegetables are good sources of vitamins and other nutrients that may protect against age-related diseases and deterioration throughout the body. Avoiding saturated fats and trans fats helps keep your arteries clear and cholesterol levels healthy, which in turn can decrease your risk of cardiovascular disease and stroke, including the small "silent"

strokes that can damage brain function. And maintaining a normal weight lowers your risk for illnesses such as diabetes and hypertension, which can harm memory.

Take Vitamins

Taking a high-quality multivitamin and individual vitamin supplements can help ensure your body is getting the nutrients it needs. Certain B vitamins—B6, B12, and folic acid—provide neuronal protection and facilitate the breakdown of homocysteine, an amino acid in the blood that, at high levels, can raise the risk of heart disease, stroke, and peripheral vascular disease.

Sleep Tight

Sleep is essential for memory consolidation as well as overall health. Although people vary in their individual sleep needs, research suggests that six to eight hours a night is ideal. Perhaps even more important than the *amount* of sleep is the *quality* of sleep. People with sleep disorders that affect breathing, such as obstructive sleep apnea, can sleep ten hours a night yet still feel unrested in the morning.

For some people, a good night's sleep can seem elusive. Developing certain habits can help: Establish and maintain a consistent sleep schedule and routine. Do your most vigorous exercise early in the day. Stay away from coffee and other caffeine sources after midmorning. Avoid excessive napping during the daytime. Shun sleeping pills unless nothing else works. And don't try to sleep if you're not tired—you'll merely set yourself up for tossing and turning.

Manage Stress

When you're under stress, it's difficult to concentrate, and insufficient concentration is one of the primary causes of poor learning and memory. Sustained stress can impair your memory by altering brain chemistry and damaging the hippocampus. Although you can't control all the sources of stress in your life, you can temper your reactions to stress.

Taking a brisk walk or exercising in other ways helps some people reduce stress levels. Listening to music, meditating, talking to a friend, or engaging in relaxing activities, such as gardening or knitting, can also help. If you can't lower your stress level on your own, you may find relief through counseling.

Stay Connected

Social support—through relationships with family members, friends, colleagues, or caregivers—can improve cognitive performance in older people. And the elderly aren't the only ones who benefit.

In a 2008 study of more than 3,600 people between the ages of 24 and 96, researchers at the University of Michigan found that across all age groups the higher an individual's level of social interaction, the better his or her mental function. A second study on the same cohort found that people engaged in social groups and those involved in solitary intellectual activities such as reading and doing crossword puzzles both scored higher in mental processing speed and working memory than the controls, who merely watched television.

Social engagement may benefit your memory in several ways. Intellectually stimulating activities often go hand-in-hand with social interaction. Social relationships can also provide support during stressful times, reducing the damaging effects of stress on the brain.

Protect Your Head

Head trauma is a major cause of memory impairment and a risk factor for dementia. Wear a seatbelt when riding in motor vehicles, as car accidents are by far the most common cause of brain injury. You can also prevent head trauma by using appropriate gear during high-speed activities and contact sports. Put on a helmet when bicycling, riding a motorcycle, in-line skating, and skiing. And wear a mouth guard during contact sports. Using this type of protective device can lower the risk of concussion by deflecting the force of a blow to the chin.

Avoid Exposure to Toxins

Reduce your exposure to toxic substances by taking sensible precautions. Read labels for safe handling before using paints, solvents, and pesticides. Test your home water supply and use a water filter to eliminate lead, if necessary. Have your car and furnace serviced regularly to minimize carbon monoxide emissions. Avoid sanding, scraping, and otherwise disrupting lead paint in older homes. If you plan to remove lead paint, hire a government-approved contractor.

Pursue Your Passion

The pursuit of an abiding passion encourages you to seek new knowledge, connects you with people who share your interest, guards against depression, and serves as a buffer against stress, all of which benefit memory. Participating in something meaningful, particularly in the context of giving to others, also helps engender a sense of personal efficacy—and the ability to make a difference can make all the difference to the health of your brain. ■

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Bearing witness fosters healing among survivors of childhood sexual abuse. *by* JUDITH LEWIS HERMAN

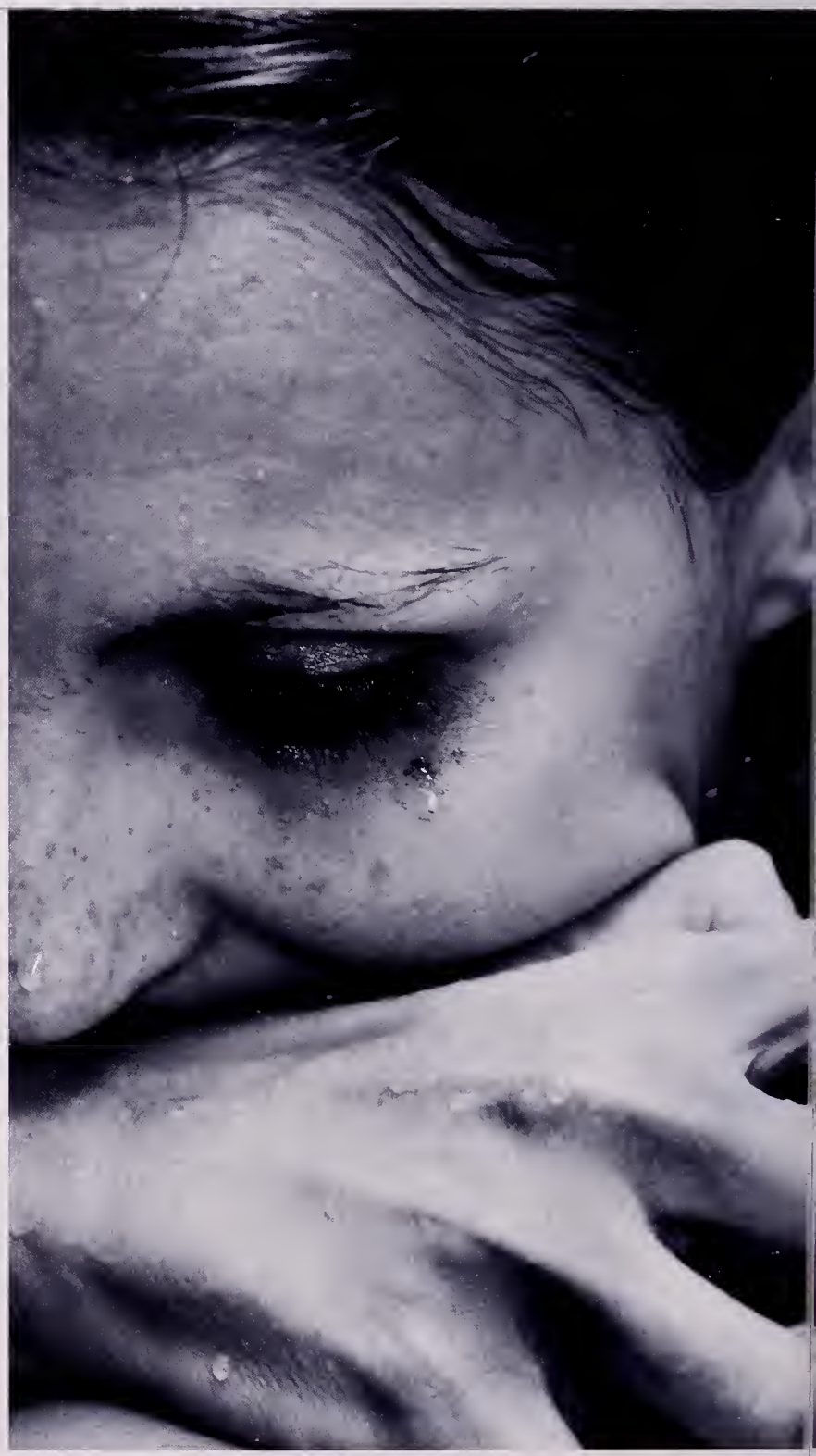
SPEAK, MEMORY



IN 1970, THE YEAR I BEGAN MY psychiatric residency, I belonged to a consciousness-raising group known as Bread & Roses Collective No. 9. In those early days of the women's movement, many women came forward to disclose sexual violations long kept secret. With a new awareness, I listened to the stories of my first patients, two women whose lives were tormented by memories of incest.

These women and their stories had a powerful impact on me. After my residency, I began working at a storefront women's clinic. Before long, a colleague and I had collected 15 cases of father–daughter incest. We first published our findings in a women's studies journal in 1977. In the year before the article was published, the manuscript was passed hand-to-hand like underground literature, and we began receiving letters from women throughout the country. They all wrote, "I thought I was alone." It was then we realized that we had indeed made a discovery.

TODAY if a child discloses sexual abuse, there is a much better chance that the person hearing the story will respond in a protective way.

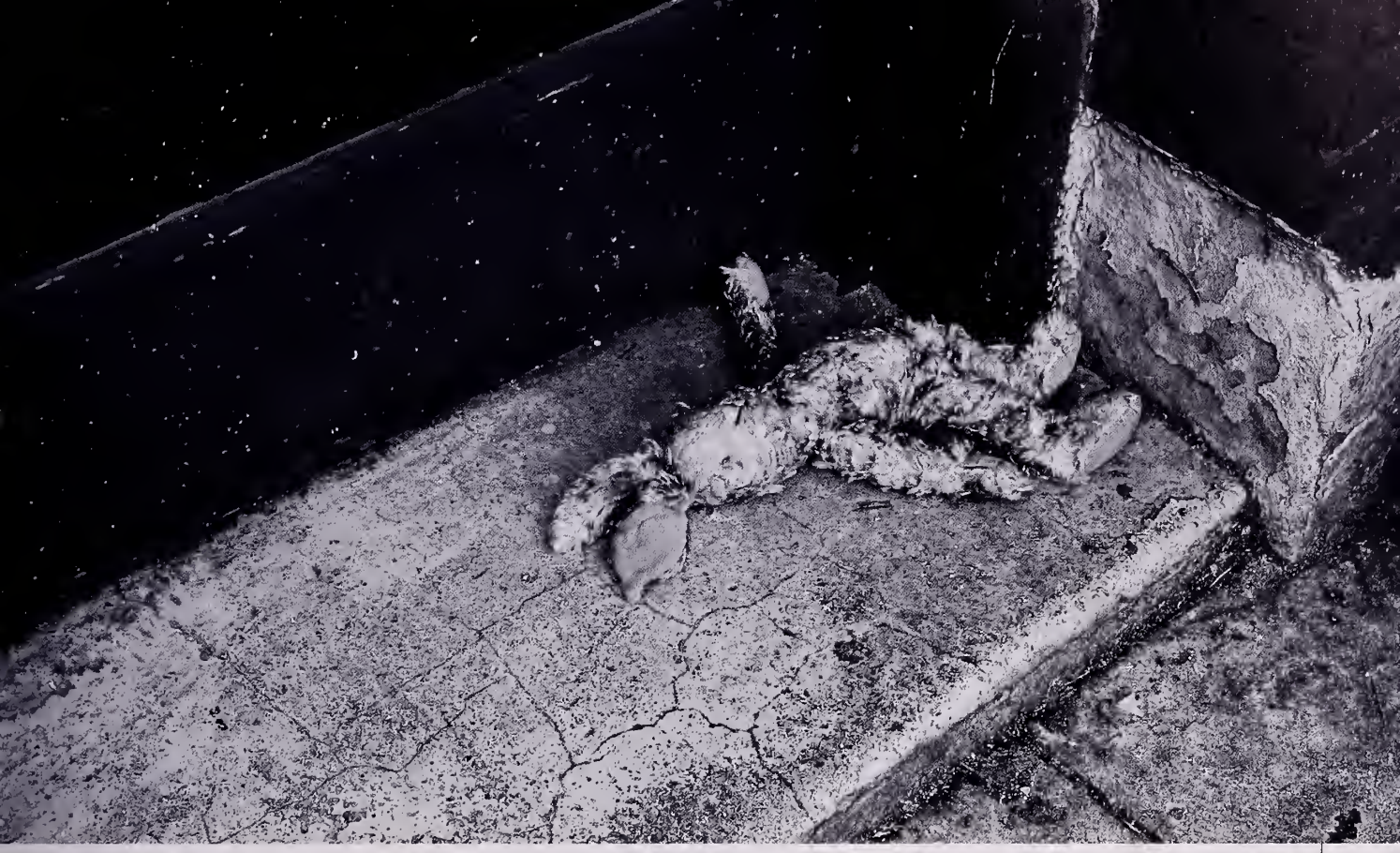


At that time, the *Comprehensive Textbook of Psychiatry* estimated the prevalence of incest at one case per million. This estimate proved to be wrong by several orders of magnitude. We now know that sexual abuse of children is common and often has terrible consequences for the abused child. We also know that the most common perpetrators are people the child knows and trusts: teachers, coaches, clergy members, uncles, brothers, stepfathers, and fathers. (The great majority of perpetrators are men.)

As the women's movement encouraged survivors to come forward, and as new research documented the prevalence of such abuse, we entered a period in which these discoveries gained sympathetic attention from the media. Oprah Winfrey set an example by coming out as a survivor of childhood sexual abuse, and she has gone on to do what I regard as some of the best public education on child abuse and violence against women. School-based educational programs were developed to encourage children to tell someone if they were being abused.

Today, if a child discloses, there is a much better chance that the person hearing the story will respond in a protective way, rather than shaming and silencing the child. Recently, the many survivors of sexual abuse perpetrated by clergy—not only Roman Catholic but Jewish and Mormon, among others—increased the credibility of victims by coming forward and enduring the rigors of court testimony to share their stories.

As long as victims of sexual abuse were shamed into silence, these crimes against children were essentially crimes of impunity. As public awareness of the problem grew, however, many states began to amend their laws to make it easier for child victims and adult survivors to testify in court. In particular, many states extended their statutes of limitations in recognition of the fact that adult survivors might need time to gain an understanding of the harm done



to them, either because they might not have initially made the connection between their suffering and the abuse they endured, or because they might have had a period of frank amnesia.

And thus began the controversy over memory. A backlash can be expected whenever crimes of impunity suddenly become crimes with possible consequences. We see this in societies emerging from repressive regimes, when perpetrators of political crimes—previously immune as government workers, police officers, spies, or prison guards—are suddenly exposed. As the evidence of their crimes accumulates, they resort to impugning the credibility of their accusers. It is no different with crimes against women and children.

As adult survivors of incest started to come forward in court, perpetrators countered that their accusers must have been brainwashed. In this rendering of the story, the accusers had been alienated from their loving families by unscrupulous psychotherapists who had instilled false memories of abuse. In a climate of sympathy for the victims, blaming a third party was generally a more favorable strategy than attacking the victims directly. It also served to patronize and demean the victims, as it implied that they didn't know their own minds.

When allegations of false memories started to appear, the media latched onto this novel angle for a while. We no longer see much in the press about false memories, but at the height of the controversy, the main line of attack was the suggestion that incompetent or biased clinicians were *implanting* memories in the minds of the vulnerable: children and unstable women. After all, why had the victims not mentioned the crimes earlier? Much was made of the notion that memories of sexual abuse disappeared from consciousness only to be recalled at some later time. The implication was that a memory recalled after a period of amnesia was inherently suspect.

In fact, many survivors of childhood sexual abuse dearly wish to forget—but cannot. When these people begin to describe the abuse, they will say something like, "I never forgot, but I was too ashamed to say anything about it. I tried to force myself not to think about it." Well into adulthood, some victims feel so tormented by their shame that they cannot give voice to what they have always perfectly well remembered.

Others may have partial recall. One patient of mine, for example, initially claimed she had no memories. What she meant was that she did not remember the details of physical encounters with her father. She did have clear memories, however, that her father would leave pornography around for her to see, that he would continually tell dirty jokes, and that his lewd interest in her and other young women was apparent in many ways. His behavior was tolerated within the family; he was just being his quirky self. No alarm was raised, and no one sought to protect her. The patient felt alone with her feelings of disgust and humiliation. So in fact, she did have plenty of memories, but she had not yet learned how to make sense of them. As she explored the feelings her memories evoked, she was able to recall more details of specific incidents of abuse.

Run Silent, Run Deep

A significant minority of victims do seem to have dense amnesia about their abuse for a period of time, only to recall it later, often through struggle and pain. In a study that Emily Schatzow, a lec-

WHEN a person is traumatized, the memory of the trauma is laid down in an altered state of consciousness.

turer on psychiatry at Harvard Medical School, and I conducted with 53 female outpatients, we found that 28 percent reported a period of severe memory deficit. What seemed to set this group apart is that the abuse began very early, in the preschool years, and ended before adolescence. Also, the degree of amnesia seemed to be related to the level of frank violence that accompanied the abuse: the more violent the abuse, the greater the memory deficit.

Two factors may be at work here. First, the memory functions of early childhood differ from those that develop later. Second, traumatic memories are not stored in the same way that ordinary memories are. Both of these factors serve to keep the knowledge of being abused out of the autobiographical narrative that each person ordinarily assembles.

In the nineteenth century, Pierre Janet, an early student of trauma, described traumatic memory as an *idée fixe*. He contrasted this with normal memory, which he described as "the action of telling a story." A memory is not truly a memory, he said, until it has been recited to oneself and to others and taken its place in our personal narrative. Ordinary memory, Janet held, is fluid, contextual, and autobiographical; it requires a certain amount of verbal processing and is subject to voluntary retrieval. A traumatic memory is static, fragmentary, and nonverbal—one remembers sights, sounds, smells, and tastes—and it is not subject to the usual mechanisms of voluntary recall. It might intrude, unwanted, as a flashback; when sought, it might remain inaccessible.

Janet's description of trauma and memory has held up extraordinarily well to the scrutiny of contemporary research. In the fourth revision of the *Diagnostic and Statistical Manual of Mental Disorders*, amnesia for all or part of a traumatizing event is recognized as one of the diagnostic criteria for post-traumatic stress disorder.

When a person is traumatized, the memory of the trauma is laid down in an altered state of consciousness. For effective retrieval, the person must gain access to that altered state, not only recalling the event, but also reconnecting with the state of feeling that accompanied it. Early in his career, Sigmund Freud used hypnosis to gain that access. In the many wars of the twentieth century, military psychiatrists discovered that hypnosis or the administration of sodium amytal could help shell-shocked soldiers access their memories. Military psychiatrists also found that "the action of telling a story" could bring dramatic relief to traumatized soldiers, often allowing them to return to battle.

As the role of early sexual trauma was being rediscovered three decades ago, many clinicians, like military psychiatrists, were eager to get to the core of the problem quickly. Since then, clinicians have become wiser. We have learned not to ask leading questions and to permit victims to deal with their memories at a safe pace.

Various methods have been developed to facilitate the recovery and integration of traumatic memories. Any of these approaches may have value—but highly specialized techniques are not necessary. What is needed most is a relationship of empathic witnessing. This therapeutic relationship creates a safe context for exploring traumatic memories, allowing for the expression of intense feelings of fear, rage, and shame, so that the memories can at last be integrated into an ongoing life narrative. In this process the amnestic barriers, which are always semipermeable, gradually give way. Then, the trauma can be grieved and allowed to take its place in the past.

This healing process may help the individual survivor come to terms with a past abusive experience, but it does not address the larger social problem of justice. Memory is not only a personal matter; as we discovered in our consciousness-raising group, it is also a matter of bearing witness.

Recently, I conducted a study in which I interviewed survivors about their visions of justice. What they wanted most was acknowledgment, both of what had happened to them and of the harm done. They also wanted the family or the community they had lived in to take some responsibility for the neglect that permitted the abuse to occur, and to make amends. Just about half wanted an apology from the perpetrator, and then only if it was accompanied by genuine empathy and remorse, as rarely as those emotions may occur in abusers. As one survivor put it, "Perpetrators lack empathy, or they wouldn't commit abuse in the first place."

Interestingly, few of my informants embraced a retributive idea of punishment for its own sake. No one wanted the perpetrator locked up, *unless* he was considered a recidivist predator. For example, one of my informants had notified the police when she discovered that her niece was being abused, just as she and her sisters had been abused in childhood by the same perpetrator. At that point she mobilized her sisters, and they supported the niece in pressing criminal charges. The perpetrator was convicted and sentenced to prison, where he finally acknowledged the abuse. My informant believed prison was the best place for him because he was still a danger to the community. To this survivor, only the desire to protect others made the ordeal of court testimony worthwhile.

Justice Deserved

Despite legal reforms, the U.S. justice system continues to be unfriendly to adult survivors and even more stress-filled for child victims. If you wished to design a mechanism for exacerbating symptoms of post-traumatic stress dis-



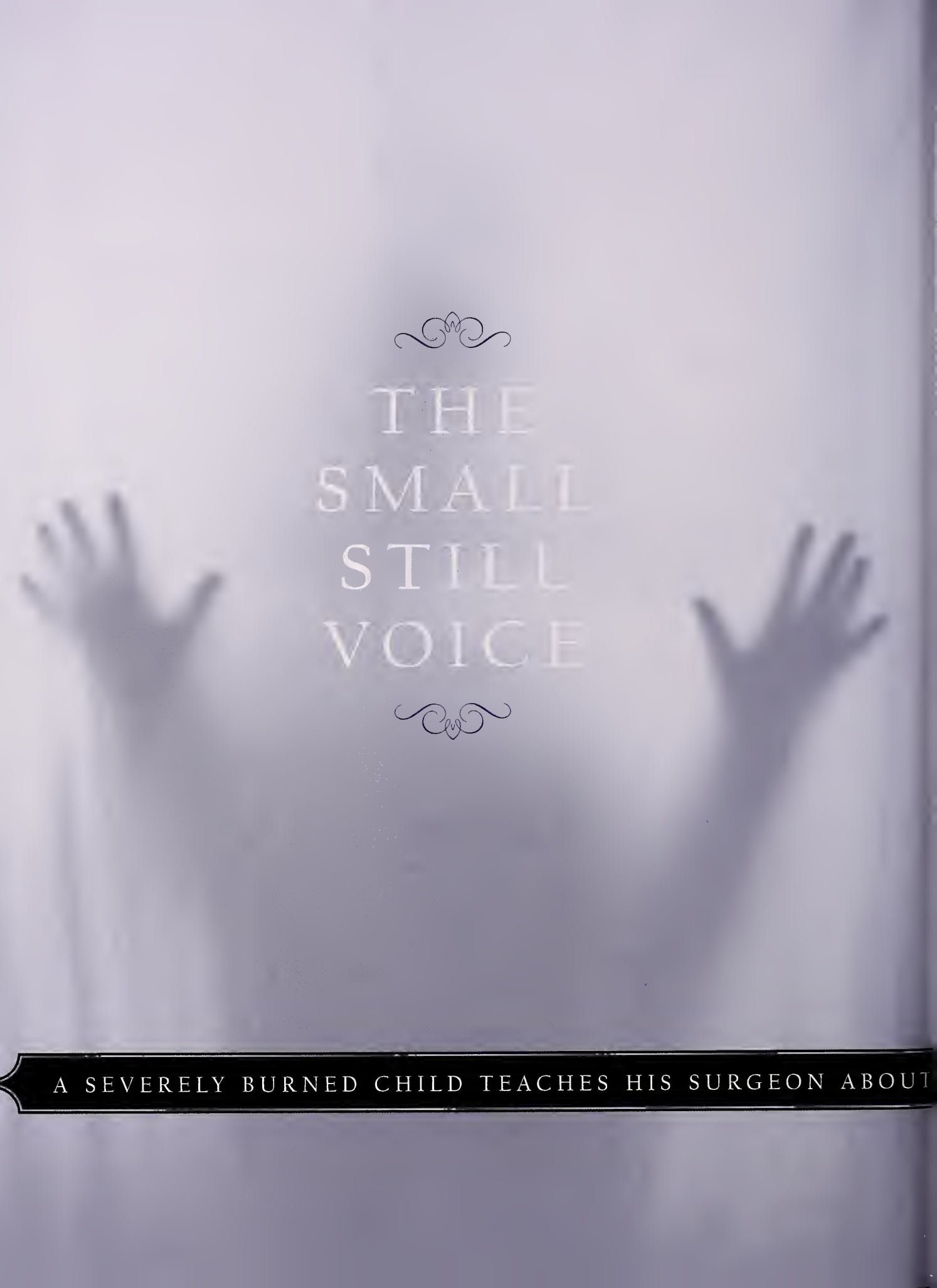
order you couldn't do better than a court of law. The adversarial system, of necessity, places the victim's credibility under attack. Instead of being able to tell their stories in their own fashion and at their own pace, victims must answer rapid-fire, yes-or-no questions, and instead of having control over exposure to reminders of the trauma, they have the reminders pressed upon them. It takes amazing courage for someone who has grown up with a perpetrator who was both loved and terribly feared, who was viewed as all powerful in the way that a child sees a parent as all powerful, to confront that person in a court of law.

More victims would risk such a confrontation, though, if the remedy the court afforded was anything resembling what victims wanted. But punishment of the offender is not what most are seeking. Moreover, there's little evidence as to the overall effectiveness of punishing and registering sex offenders. Criminal prosecution simply doesn't work as a prevention strategy. For this reason, it is worth considering some emerging models of community intervention that differ considerably from conventional legal responses. Conceptually, these models draw their inspiration from the restorative justice movement.

One of these models, initially developed in a child-protective service in Canada, is called family group conferencing. In this model, all the members of a family are brought together for a formal meeting, each with at least one support person. In this way, an extended social network may be mobilized. Older children are included in the process and may bring a friend. The meeting begins with a full discussion of what happened and an acknowledgment of both the facts of the case and the harm done. Child-protective officials also lay out the requirements for an action plan to remedy the situation. The family group must then devise a plan to protect the child victim from further harm. An agreement is signed, and the respective support systems agree on to how it will be monitored and enforced. In this process, punishment of the perpetrator is beside the point. The victim's priorities are central, not peripheral, to the outcome, and the victim's community takes responsibility for protective action.

Mobilizing a community response may ultimately do more to develop a culture of protection and safety than prosecutions can accomplish. The primary need, of course, is protection. For children the first line of protection appears to be a mother with the power to take care of them. It has been clear even from our earliest research on incest that a disabled or disempowered mother is one of the biggest risk factors for child sexual abuse. Any policy or intervention that promotes women's health and enhances the status of women ultimately protects children as well. The same women's movement that brought this problem to light is also the surest advocate for its solution. ■

Judith Lewis Herman '68 is a clinical professor of psychiatry at Harvard Medical School and director of training at the Victims of Violence Program at the Cambridge Health Alliance in Massachusetts.


THE
SMALL
STILL
VOICE
A SEVERELY BURNED CHILD TEACHES HIS SURGEON ABOUT

OUR LIVES HOLD TRANSFORMATIONAL moments, fragile as spun glass. They drift for only a second and then shatter. We don't just *feel* these revelations. They hit us, like a fist. One such moment occurred for me halfway through the first year of my surgical residency, during a two-month stint on the burn service at Massachusetts General Hospital.

All residents dreaded the burn service. The adult ward was bad, but the pediatric ward, known as the Shrine, was far, far worse. The Shriners Hospital in Boston served as the major center for most pediatric burn victims along the eastern seaboard. Its burn service, which the surgical residents had grimly nicknamed Crispy Critters, was the closest thing we could imagine to hell on earth. There, dozens of mutilated, suffering children huddled in one somber, sorrowful building.

On my first day, the head nurse led me to the intensive care unit to see the big burns—"the eighty-percenters or higher." Before going onto the unit, we had to don masks and sterile scrub suits with hoods. As the translucent glass doors hissed apart, we entered into an alien world—an encampment. The room was bathed in the purple glow of ultraviolet lights. Each child was surrounded by huge plastic drapes designed to wall out bacteria. Devices made whining, sucking, and bubbling sounds, a robotic chorus that rose up around each swaddled form. Each child resembled a mummy; only the shape outlined beneath layers of dressings hinted that a child might lie buried within. Had it not been for the frenzied activity of the machines, there would have been nothing to suggest the larval forms were even alive.

I had never seen so much suffering concentrated in one place. How would I get through the rotation? It seemed unendurable.

PHOTO: LUCKYPIX PHOTOGRAPHY/VEER

I THE ENDURING POWER OF THE SPIRIT. ~ *by Allan J. Hamilton*

The nurse led me out of the ICU, known affectionately as Mummy World, and into Camp Chronic, the ward where survivors eventually arrived for endless rounds of reconstructive surgery. Here the children became living clay as surgeons practiced the dreadful artistry of reconstructive surgery. And here the children began to emerge. Like geologic formations, they became sedimentary, surgical layers, recording each new technical era, one upheaval to the next.

It took me weeks to settle in. At first I felt relief whenever I could leave the building and breathe lungfuls of antiseptic-free air. I would gaze at people walking down the street, with bodies like supple saplings and hands as smooth and perfect as porcelain. It amazed me how utterly normal the physical world was outside. Entering Crispy Critters each day felt like being condemned, with my heart drowning as soon as I passed through its doors.

After some time, I began to view things differently. Every child became a small, brave experiment in courage, endurance, and improvisation. Gradually, Crispy Critters seemed less like a bleak prison and more like a hybrid of laboratory and chapel. Life had been rendered to molten form. Child after child was recast into an angel and then sent to test the world's compassion. And we—the outside, unmarred world—repeatedly failed the test.

Fallen Angel

One angel-child stood out for me. His name was Thomas. His story, like those of so many in the institute, had a grim beginning. When he was about ten years old, he and a friend were playing in the rolling farm country outside Lancaster, Pennsylvania. They walked across fields that were pushing up the green promise of the season's first corn. From there, they passed through the edge of a family farm. As they hiked, they came across a footpath to the crest of a large hill, upon which sat a tower carrying a high-voltage line. They scaled the tower, which commanded a view of the whole countryside. From its heights, the boys could see not only their own houses but horizons far beyond.

What a view it must have been! For a moment, they must have felt like eagles. But Thomas slipped. He fell about a dozen feet and came to an abrupt halt. His clothes had caught on one of the arms of the tower. As he reached up to pull himself off, he touched the power line. Thousands of volts arced through his small body, shaking it convulsively. His body tore loose from its snag, but not before his clothing had ignited. He plummeted more than a hundred feet to the ground, a flaming meteorite. His companion clung to the electric tower, too terrified to move.

Smoke rising over the horizon alerted firefighters. They lowered Thomas's friend safely to the ground. Of Thomas, there remained little that was not burned. Small patches of skin remained intact only in his armpits, his groin, and the folds of certain joints. It seemed as if every bone had been broken. Nearly all his soft organs were damaged and bleeding. No one held much hope the boy could survive. Mercy suggested that dying might have been gentler.

Thomas's life, though, continued to flicker. The paramedics stabilized the boy and rushed him to a trauma center in Philadelphia. There he underwent three operations to stem the internal bleeding. Then a special medical turboprop aircraft flew him to Boston, where an ambulance sped him to the Shrine. He arrived ready to enter Mummy World, swaddled from head to toe in gauze. Intravenous lines poked through his dressings like unruly vines. That was when he became my patient.

A Fresh Start

In the initial phases of critical burn care, the patient must be covered with new skin. This is accomplished first with grafts taken from fresh cadavers. Although the skin is dead, the thin strips of dermis and epithelium work beautifully as temporary skin. Soon the patient's immune system will reject the foreign tissue, but, with luck, the cadaver grafts will buy the time needed for harvesting the patient's skin—the autologous skin—and using it to resurface the body.

Thomas's body had an unusually potent proclivity for rejecting cadaver grafts. While most patients rejected a graft in ten to fourteen days, Thomas would slough his off within five. We'd have to find more skin in the hospital's tissue bank, then resurface his body again. Each time the procedure required six to eight hours of tedious work to suture the new skin grafts into place.

The surgery was painstaking and wearying. Skinning a human corpse and sewing new skin into place like upholstery fabric are gruesome tasks. But we could do little else to save Thomas's life. He rejected the second series of grafts in just four days. We undertook a third set, and a fourth set. The latter lasted less than 48 hours.

It seemed unlikely that Thomas would survive. We simply couldn't harvest enough native grafts to cover his entire body quickly enough. We were ready to give up on him, more out of exhaustion perhaps than pity. But fate intervened. The boy's parents had been devastated by what had happened to their son. To be isolated in Pennsylvania, while their son's life slipped away in Boston, proved to be too much. Thomas's father, only 42 years old, collapsed from a heart attack and died.

Thomas's mother called to let the surgeons and nurses know her husband had passed away. It seemed just too much tragedy for anyone to bear. But his mother calmly asked whether we would be interested in harvesting skin grafts from her husband's body.

The idea had merit. Thomas's condition had continued to worsen, and he was slipping deeper into his coma with each bout of graft rejection. His body was already becoming peppered with small abscesses and sites of local infection,



signs that the latest cadaveric grafts would soon be shed. But skin from Thomas's father might not be rejected. It would not be autologous tissue, but it would be close. It was worth a shot.

A Kindred Spirit

Our surgical team flew to Philadelphia with crates of instruments. It was difficult to imagine any relationship between the gray, cold body of Thomas's father and the other, near-lifeless body in Boston. Yet we sliced the skin as thinly as we could, packed the translucent strips in sterile plastic bags, and placed the bags inside a refrigerated cooler for the return trip.

At the Shrine, more bad news awaited us. During the night, Thomas had worsened significantly. Bacteria were growing in his bloodstream. He was slipping into a terminal, septic coma. We felt like fools, stranded on the beach with our picnic cooler full of skin. It seemed a grim, futile joke.

In the coffee-break room at Crispy Critters, we debated endlessly. Should we just freeze the father's skin and keep it in the unlikely event that Thomas

"MY DAD'S JUST STANDING THERE AT THE END OF MY BED.



survived? Finally, hope prevailed. The senior surgical attendings made the decision: We would cover Thomas with his father's skin.

That morning we removed all the dead graft tissue covering Thomas. Painstakingly, over the next eight hours, we quilted his father's skin onto him. The grafts looked lifeless and gray. I had little confidence.

By dinnertime, we had finished. Fresh bandages in place, Thomas's comatose body was wheeled back into its slot in Mummy World. His vital signs seemed stable enough. We knew he had survived considerable surgery, but we had doubts about his physiologic reserves. I went into the call room and fell asleep instantly. I had been on the move for more than 48 hours.

Only seconds seemed to have passed before I woke up, angry and disoriented. A nurse was pounding on the call-room door. I looked at my watch. I'd been asleep for only two hours. Thomas was probably dying. Maybe his heart had already stopped. I steeled myself. We'd done everything possible. It was time to let go.

I opened the door. "It's, it's Thomas," the nurse stammered. "He's, he's trying to talk!"

That simply wasn't possible. Thomas must be having problems with his ventilator. She'd misinterpreted his respiratory efforts as an attempt to talk. Hadn't he been in a coma for nearly a month?

I ran to the ICU. Not only was Thomas trying to speak, but he was also moving all his limbs—something he'd never done before. He was fighting his bandages and constraints. It must have been extremely painful, as many of his fractures hadn't yet healed. But the efforts were unmistakable. He was trying to pull out his endotracheal tube.

I slipped my hands inside the plastic-encased arm ports, reached around his throat to undo the knot, and deflated the small balloon at the end of the tube. Then, daring more than hoping, I pulled the tube out of his mouth.

He coughed violently a couple of times. Suddenly, he spoke. His voice was perfectly clear.

"What happened to my father?"

No one had uttered a word to Thomas about his father; he'd been unconscious the entire time. The nurses looked at me. It was my responsibility to answer. After all, I'd been the one who'd removed the boy's endotracheal tube.

I decided to lie. "Nothing has happened to your father, Thomas. He's just fine," I said.

Thomas looked at me in confusion. "Are you sure?" The boy was completely lucid.

"Yes. I'm sure. He's fine. He'll be glad to hear you're getting better."

Today, I deeply regret that lie. I should have told him the truth right away. I was a young resident, though, and I didn't know better. I thought I was being kind. But Thomas knew something was wrong.

"My dad's just standing there at the end of my bed. Why doesn't he say something?" There was the hammer blow.

For a crazy instant, I blanked out what had actually happened. The father's death. The harvest of skin. Then reality returned. Thomas must be seeing someone through the plastic, a distorted silhouette that reminded him of his dad. I looked around. No one was there. Just the drapes and the lights beyond.

"Thomas," I asked, choking back tears in disbelief, "where do you see your father?"

"He's standing right there," he answered, staring at the empty foot of the bed. "Hi, Dad!" he called out, and he feebly attempted to wave.

One of the nurses choked back a sob.

"Thomas, your dad passed away," I said. "He died three days ago. He had a heart attack."

I could see the shock registering within, even beneath so many layers of bandages. Then I heard him whisper something. I leaned over.

"That must be his ghost then that's waving back at me," he said softly.

I knew then that what Thomas saw at the foot of his bed was his father's spirit. Here was my own fragile moment of awakening. It left me tingling, as if sparks were dancing off my skin.

Body and Soul

Thomas improved. He didn't reject his father's grafts. And over the next month, a researcher at the Massachusetts Institute of Technology announced a new research method to harvest epidermal cells. The patches of skin required for this experimental technique were exactly like those Thomas still had intact. Harvested cells from these patches were taken to the laboratory, induced to grow, and spread atop a layer of denatured collagen. Eventually, the cells would coalesce on the collagen sheet, which could then be grafted directly onto the patient. Since the original cells were all derived from the patient, there was no risk of immunologic rejection. Thomas was among the first patients to undergo this procedure. His survival was, in effect, the culmination of a long sequence of miracles.

As the months passed, Thomas grew strong enough to graduate to Camp Chronic. There he endured the usual series of surgical revisions. His fingers were gone, and his reconstructed hands looked like something akin to lobster claws. His new nose—constructed of fat and muscle from his scalp, then covered with a graft patch of skin—was more a piece of fleshy caulking than elegant reconstruction. It covered a terrible gap, irreconcilable with our usual notion of facial symmetry and composition. But Thomas was alive, against all odds. And his spirit was clear and bright.

If anything, Thomas's spirit shone brighter than those of others. He became indomitable. Where hundreds of kids had faltered, he would not. He was adamant about returning to public school outside Philadelphia. Then the prosthetic shoes on his feet failed. Both legs became infected, and he needed to have bilateral amputations below the knee. It took four more months to learn to walk again. But he did, and then he asked to return home, back to school.

It took seven more years to complete my neurosurgical training. I didn't see Thomas again until the last day of my final year as resident. I was on the elevator. In the corner stood a horribly disfigured, diminutive person. I suddenly recognized the attractive woman standing alongside him. It was Thomas's mother.

Thomas didn't remember me at all, but his mother did. She bragged that he was an honor student now. And she wept as we departed, telling me how grateful she was for what we had done for him. Thomas waved goodbye to me with a misshapen hand I had probably helped build.

But as he waved, he smiled at me. A big smile! A real smile! The smile of someone genuinely happy to be alive. Then I realized I had received a great gift on this last day of my surgical training. I had been brought into a great, full circle. I had seen the hell of Crispy Critters. I had learned to see beyond the burns and the deformities to the real children who lived and thrived there. I had been permitted to experience the transformational moment when the spirit of Thomas's father had come from beyond the realm of the flesh to intervene, to protect, and maybe even to guide us as we took care of his son. Now I had been permitted to grasp the miracle from beginning to end, its entire sweep across time and space.

As I saw Thomas smile and wave, I reminded myself that I had been permitted to watch the mortal threads of my life interweave with the strands of the spiritual powers in Thomas's life. The trip had lasted precisely the span of my eight-year surgical training. That could not have been mere coincidence.

I understood, for the first time, that the filaments of my own existence were inextricably interwoven with Thomas's, his father's, his mother's, and those of a host of other individuals. An idea began to take shape: I could see thousands of orbits, mortal and spiritual, all spun from the luminous fabric of creation. My eight-year-long adventure was not just the story of a surgical residency. It was a message: We're never solitary mortal beings. Supernatural comfort is all around us—like the spirit of Thomas's father—and never leaves us alone without divine strength and protection. But without the certainty of our link to the supernatural, the burden of our individual existence can make us crazy. Thomas's experience made me realize that suffering is the background, the context, against which we discover love's power over death, over illness. Suffering is what lends love its supremacy over death. ■

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CAMPING OUT: Soldiers who contracted malaria while serving on Guadalcanal during World War II were sent to field centers for treatment and recovery.

FEVER PITCH

A physician recalls his work in a World War II



In the last years of World War II,

I played a small part in what may have been one of the largest medical research projects of that war. Our goal was formidable: to conquer malaria, a disease many thought was unconquerable. We did not, unfortunately, achieve that goal. But the story of our project may interest, perhaps even encourage, contemporary researchers while also providing a picture of the concerns, setbacks, and small triumphs that were part of what was known as the Malaria Project.

In the Heat of Battle

It was apparent early in the war that malaria was going to be a scourge to Allied troops, especially in their operations in North Africa and the Pacific. By 1942, the illness had incapacitated half of General Douglas MacArthur's active-duty forces in the Southeast Pacific, hobbling the commander's efforts to advance north from Australia and New Guinea. By the war's end, an estimated 60,000 military personnel had died of malaria in those theaters.

One reason the casualty numbers were high was the lack of an available, effective treatment. Prior to the war, quinine was the most common antimalarial in use. Extracted from the bark of cinchona trees, quinine had originally been harvested from wild trees in the jungles of South America. Since the eighteenth century, however, the drug had been produced from trees cultivated on plantations throughout Southeast Asia. When this region came under Japanese control in the 1940s, the world's access to quinine was cut off.

Synthetic alternatives were limited; quinine's effectiveness and low cost had squelched profitability—and thus research—prospects. Although there had been some development in the 1930s, the results, such candidates as chloroquine and atabrine, sat untested on the shelves of manufacturers, including I. G. Farben in Germany and

research project aimed at stamping out malaria. *by* CURTIS PROUT



PRICKLY SITUATION: U.S. troops serving with army engineers during World War II give blood for tests to prevent malaria attacks in tropical regions.

Winthrop Chemical Company in the United States.

The quinine blockade and the toll malaria was taking on U.S. troops spurred the U.S. Office of Scientific Research and Development, or OSRD, to initiate the Malaria Project in 1942. The project enlisted a stellar list of U.S. researchers, including infectious disease expert Lowell Coggeshall and immunologist Michael Heidelberger.

I first learned of the project in December 1943. I was a junior resident at the Johns Hopkins Hospital and had been summoned to the office of Warfield Longcope, the physician-in-chief. I was nervous, fearing a reprimand for some medical error I had unknowingly committed. But my worries were short-lived as Longcope began by telling me of an urgent call for researchers ineligible for military service and qualified to work on a project aimed at finding a cure for malaria. Would I be interested?

I accepted immediately. I had expected to head for the tropics for this research but soon learned that decision makers in Washington, DC, felt that the factors of immunity or partial immunity in areas endemic for malaria would interfere with the evaluation of any antimalarial medications. The project's five clinical testing areas would instead be stateside. I was given a choice between the state prison in Joliet, Illinois, and the Boston Psychopathic Hospital, which was later renamed the Massachusetts Mental Health Center. With my wife and our two small children in Boston, I naturally chose the latter.

The Boston unit was headed by Allan Butler '26, a professor of pediatrics at Massachusetts General Hospital, and supported by two senior physicians at the hospital: Augustus Rose '32 and Lawrence Trevett. The unit's personnel roster was rounded out by three young physicians eager to help the war effort: Arthur Linenthal '41, Joseph Hindle, and me.

The unit's testing facilities were split between Boston Psychopathic and a ward at MGH. At MGH, Linenthal was to test and observe any effects of the antimalarial candidates on conscientious objectors who had agreed to work at the hospital in lieu of being forced into the military—or jailed for their refusal. At Boston Psychopathic, our unit was to test the effectiveness of the antimalarials against the disease itself. Our subjects were psychotic patients selected from the populations of the dozen or so large hospitals overseen by the Massachusetts Department of Mental Health. Hindle and I were assigned to this hospital.

The Good, the Bad, and the Ugly

The idea of using psychotic people as test subjects for malaria research was ingenious, bizarre, and, especially by today's standards, unethical. With what justification could we give a dangerous infectious disease to these people without informed consent? Well, at that time there were no ethics committees, and a standard for informed consent in biomedical research had yet to be broadly articulated; The Nuremberg Code, an outcome of the era's war-crimes tribunals, wasn't assembled until 1948.

But there was a solid scientific rationale to this approach. Before penicillin, 10 percent of all patients in the mental hospitals in the developed world were suffering from late syphilis of the brain, known as general paresis of the insane, or, simply, paresis. Arsenic and bismuth, moderately effective in other forms of syphilis, did not affect paresis. In Vienna in 1917, Julius Wagner-Jauregg observed the effects of malaria on people with paresis; some paretics who contracted malaria improved greatly. His work resulted in cure or improvement for many thousands of psychotic paresis sufferers and earned him a Nobel prize in 1927. At the time, it was thought the illness's fever was effective against paresis, but later investigations showed the effect was probably a result of immunity to antigens shared by the treponema of syphilis and the malaria parasite.

By the 1930s, hospitals throughout Europe were administering malaria to paretic patients with encouraging results. In this country, the center for malaria therapy for paresis was the Johns Hopkins Hospital. By the 1940s, when OSRD was deciding how to structure the Malaria Project, the malaria treatment of paretic patients, in which quinine was used to successfully terminate the infections, was an accepted standard.

OSRD studied the procedure and approved the use of paretic patients. The project was to use an allegedly "tame" strain, and quinine was to be kept on hand should the experimental medications previously tested on the conscientious objectors prove ineffective at stemming malarial infections. Although

PHOTOS IN THIS ARTICLE AP PHOTO

WHEN THE FEVERS began to cycle every 48 hours and the parasite counts reached a predetermined level, we would administer an experimental drug that had been tested on the conscientious objectors.

decision makers in Washington may have harbored objections to the ethics of this approach, the urgency of the wartime situation trumped their concerns.

Into the Breach

The antimalarial candidates, and even the malaria strains we tested on the subjects in our unit, came out of the research laboratories of pharmaceutical companies, academic chemistry departments, and at least one cosmetic manufacturer. Approximately 13,000 candidate compounds were developed for the project; most were hastily tested for toxicity in animal models. Malaria strains were also tested; avian strains were evaluated in domesticated fowl, and human strains were tested on dogs and monkeys. The outcomes of these trials, unfortunately, were rarely shared with the clinicians who administered the candidate antimalarial agents. In addition, compounds effective against animal malaria were usually not effective against the human form and vice versa.

Once we had administered the candidate compounds to our group of conscientious objectors and had inoculated our paretic patients with malaria and provided them the selected antimalarial, we focused on monitoring the effects of the agents. Linenthal would monitor his charges for changes resulting from the antimalarials, and Hindle and I would check our patients for disease progression after treatment.

The daily routine at Boston Psychopathic wasn't arduous. We would carry out daily rounds, physical examinations, blood counts, and parasite counts for which I devised a logarithmic scale for charting the daily levels. From time to time, one of the senior hospital physicians, either Rose or Trevett, would come by for rounds, and once a week, Butler would meet with Linenthal, Hindle, and me before departing to Washington to report on the results of our testing.

The testing protocol we followed began when we inoculated our paretic patients with an attenuated strain of *Plasmodium vivax*, the least virulent of the Plasmodia strains to cause malaria. When the fevers began to cycle every 48 hours and the parasite counts reached a predetermined level, we would administer an experimental drug that had been tested on the conscientious objectors. Then we would carefully watch parasite counts, fever, and the patient's general condition. If the disease continued unchanged after about a week, we would terminate it by giving the patients a dose of our closely guarded supply of quinine. After a suitable period of observation, most patients returned to the state hospital from which they had come, and we never saw them again.

Even today I am troubled by the fact that I never knew what happened to those patients. We perpetuated the malaria strain we used by taking blood from infected patients and injecting it intravenously into new arrivals. How many patients, I wonder, later developed hepatitis or other diseases as a result of this practice? And because *P. vivax* has been known to relapse years after its first attack, how many suffered subsequent attacks—an outcome for which, at the time, there was no therapeutic recourse?

War Stories

Although at my darkest times I felt I wasn't contributing to the war effort, our work did produce two scientific papers. One was among the first studies to show that penicillin was ineffective against malaria while another demonstrated the effectiveness of penicillin on paresis.

Some of the more interesting results were unpublished; they arose from observations of the responses that the conscientious objectors had to the various antimalarials. One example stemmed from the testing of a compound developed by Louis Fieser, a professor of organic chemistry at Harvard College, where he was also the chief liaison to OSRD. Tests of Fieser's products usually were unsuccessful, and this candidate had been no exception. Fieser, however, was unsatisfied with the results and insisted we use larger doses for longer periods than our protocols permitted. Despite his insistence, the only effect the compound induced was a deep crimson staining of the blood plasma, which caused those receiving it to look exceptionally pink and healthy for several weeks.

Another compound had a somewhat startling side effect: The hair of the 20 or so men testing it became white at the roots. And their hair continued to grow out white until the drug was stopped. Thus, some of the conscientious objectors developed a broad albino stripe that was bordered by their normal hair color—an appearance that gained them the nickname "skunks," a moniker that vanished when their original hair color grew back.

Near the end of our project in 1945, chloroquine, tested by one of the other units, was proving to be marvelously effective. We had been simultaneously testing its bromine analog. It showed itself to be as effective as chloroquine against the parasite but more costly and less safe, so it was not developed further.

More than 60 years have passed since the Malaria Project ended, and research on the disease continues. An estimated 247 million cases of malaria are reported globally each year. One million of those cases, mostly children under five years, die from the disease. It is my hope that knowledge of this project may aid science's efforts and ultimately help to conquer what still seems unconquerable. ■

Curtis Prout '41 taught physical diagnosis at Harvard Medical School and Brigham and Women's Hospital for many years, served as assistant dean for students at HMS, and was chief of medicine at Harvard University Health Services. Now semi-retired, Prout has an internal medicine practice in Manchester, Massachusetts.

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YOU MUST REMEMBER THIS:
What can Buddhist monks, medical residents, and alien abductees tell us about memory? Harvard physicians and researchers listen so we all might learn.

PHOTO: DAVID TROOD/PHOTONICA/GETTY IMAGES